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Recent advances in enantioselective copper-catalyzed 1,4-addition

Thomas Jerphagnon, M. Gabriella Pizzuti, Adriaan J. Minnaard
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A comprehensive overview of recent literature from 2003 concerning advances in enantioselective copper catalysed 1,4-addition of organometallic reagents to α,β -unsaturated compounds is given in this *critical review*. About 200 ligands and catalysts are presented, with a focus on stereoselectivities, catalyst loading, ligand structure and substrate scope. A major part is devoted to trapping and tandem reactions and a variety of recent synthetic applications are used to illustrate the practicality and current state of the art of 1,4-addition of organometallic reagents. Finally several mechanistic studies are discussed (162 references).

1. Introduction

Asymmetric catalysis is arguably one of the areas of chemical research where exquisite control over chemical reactivity and molecular recognition has resulted in levels of stereoselectivity beyond what could be imagined just a few decades ago.¹ Our ability to efficiently prepare homochiral compounds is nowadays the basis for numerous advances in the synthesis of natural products, pharmaceuticals and agrochemicals² whereas the role of chiral components in supramolecular chemistry and molecular nanoscience is rapidly increasing.³ Despite the high level of sophistication reached in for instance asymmetric hydrogenation⁴ other transformations continue to offer major challenges regarding catalyst activity, stability and selectivity as well as scope of the methodology and practicality. Among the most powerful methods in asymmetric synthesis is the enantioselective 1,4-addition of carbon nucleophiles to α,β -unsaturated compounds in which a C–C bond

and a new stereogenic centre are formed.⁵ Conjugate addition has developed into one of the most widely used methods for asymmetric carbon–carbon bond formation in organic chemistry. This transformation involves the reaction of a nucleophile to an α,β -unsaturated system activated by an electron-withdrawing group (EWG). The addition takes place at the β -carbon of the unsaturated system, resulting in the formation of a stabilized carbanion. After protonation (H^+) of the carbanion, the β -adduct is formed with a single stereogenic centre, whereas quenching with an electrophile (E^+) results in the α,β -disubstituted product with two newly created stereocentres (Scheme 1).

A typical problem associated with conjugate addition to α,β -unsaturated carbonyl compounds is the regioselectivity of the nucleophilic addition. Addition of a soft nucleophile occurs preferably at the β - or 4-position of the unsaturated system, resulting in the 1,4-adduct, while 1,2-addition is favoured if hard nucleophiles are used (Scheme 2).

The first example of an uncatalyzed conjugate addition reaction was already reported in 1883 by Kommenos where he described the addition of diethyl sodiomalonate to diethyl ethyldenemalonate.⁶ The tremendous versatility and scope of

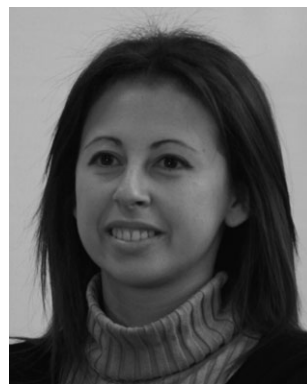
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Thomas Jerphagnon

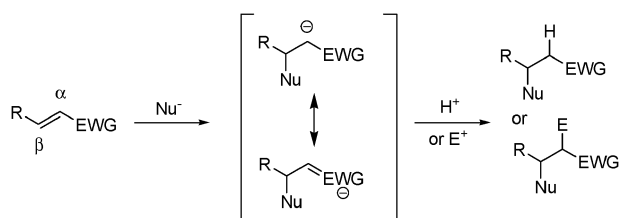
Thomas Jerphagnon was born in 1974 in Mâcon, France. He studied at the University of Bourgogne and obtained his degree in 2000. He received his PhD degree in 2003 from the University of Rennes 1, France, under the guidance of Dr C. Bruneau and Prof. P. H. Dixneuf. After working in the group of Prof. G. van Koten, University of Utrecht, The Netherlands, he joined the group of Prof. Ben. L. Feringa at the University of Groningen, The Netherlands. His work is

focused on the development of new racemisation catalysts and their application in dynamic kinetic resolution.

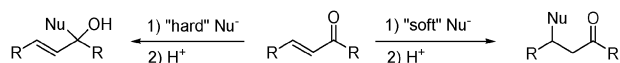


M. Gabriella Pizzuti

Maria Gabriella Pizzuti was born in 1979 in Potenza, Italy. She took her MSc in organic chemistry, in 2003, at the Università della Basilicata, under the guidance of Prof. Carlo Rosini. She received her PhD degree in the group of Prof. Ben. L. Feringa at the University of Groningen, The Netherlands, in 2008. She is currently working as Project Manager at Schering-Plough in Oss, The Netherlands.



Scheme 1 Principle of conjugate addition reaction.



Scheme 2 Addition of hard and soft nucleophiles to α,β -unsaturated carbonyl compounds.

the Michael addition using a variety of (soft) nucleophiles and the copper-mediated conjugate addition of a range of (hard) organometallic reagents, as well as various related methods, are testimony to the importance of these C–C bond formations. As the focus of this review is on copper-catalyzed conjugate addition of organometallic reagents, the reader is referred to recent reviews on related transformations. High stereoselectivities have been reached using chiral substrates, chiral auxiliaries and stoichiometric chiral ligands in copper-mediated 1,4-addition. Pioneering work on copper-catalyzed 1,4-addition of Grignard reagents to cycloalkenones by Lippard in 1988 using chiral copper(I) tropinone complexes resulted in up to 78% ee.⁷ Subsequently, a wide variety of chiral ligands and metal complexes were reported for conjugate addition of organometallic reagents including Grignard, organozinc and organoaluminium reagents, with in general only modest enantioselectivities. Among the numerous parameters that effect these often complex transformations are the nature of the metal ion, ligand structure, counterion, solvent, aggregation, as well as competing catalytic species and pathways. Design of new ligands (*i.e.* phosphoramidites and phosphines) and careful tuning of

the activity of the chiral catalyst complexes have cumulated in the first catalytic enantioselective conjugate addition of dialkylzinc reagents with absolute levels of stereocontrol by our group (1997) (*vide infra*, chapters 1 and 2, ref. 14 and 16), the rhodium-catalyzed conjugate addition of arylboronic acids by Hayashi (1998)^{8,16} and co-workers and the copper-catalyzed conjugate addition of Grignard reagents by Feringa and co-workers (2004) (*vide infra*, chapter 2.2.1, ref. 45). Transmetalation between organometallic reagents and several transition metals such as Ni,⁹ Cu,⁹ Pd¹⁰ and Ti¹¹ to generate a more reactive or softer organometallic reagent has been demonstrated in the past years and proven to be crucial for efficient catalysis. In the case of copper-catalyzed 1,4-addition of R_2Zn reagents, the alkyl transfer from Zn to Cu is a key step to form *in situ* a new organocopper species which achieves alkylation of the α,β -unsaturated compound. In the enantioselective copper-catalyzed 1,4-addition of diethylzinc, reported by Alexakis and coworkers in 1993,¹² 10 mol% of CuI in combination with a chiral trivalent phosphorus ligand was used resulting in the ethyl addition to 2-cyclohexenone with a moderate 32% ee. In 1996 Feringa *et al.* introduced novel binol-based phosphoramidites as monodentate chiral ligands in the copper-catalyzed 1,4-addition of dialkylzinc reagents with enantioselectivities up to 90% ee.¹³ This new class of chiral ligands proved to be highly efficient toward both acyclic and cyclic enones, reaching complete enantiocontrol for the first time for a range of cyclic enones.¹⁴ Organozinc, aluminium and magnesium reagents can be prepared routinely *via* metalation, transmetalation, metathesis or oxidative addition. Grignard reagents are readily available due to their easy synthesis. Several reagents are commercial *i.e.* Grignard reagents, dialkylzinc reagents and trialkylaluminium reagents. However, there is a considerable difference in price of these reagents: MeMgBr (83 euros per mol), Me₂Zn (1600 euros per mol), Me₃Al (155 euros per mol) (Aldrich, 2008) as well as the number of alkyl group that are effectively transferred. Most of these organometallic compounds are pyrophoric and water sensitive, therefore they should be handled with care.



Adriaan J. Minnaard

Adriaan J. Minnaard received his PhD degree from Wageningen Agricultural University, The Netherlands. He was a scientist at DSM-Research in Geleen, The Netherlands, from 1997 to 1999. Subsequently, he joined the University of Groningen in 1999 as an Assistant Professor in the department of Prof. Ben L. Feringa. In 2005, he was appointed Associate Professor and in 2006 he was a guest researcher in the group of Prof. H. Waldmann at the Max Planck Institute for Molecular Physiology in Dortmund, Germany. Currently he is leading the department of Bio-Organic Chemistry. His work focuses on asymmetric catalysis and natural product synthesis.



Ben L. Feringa

Ben L. Feringa obtained his PhD degree in 1978 at the University of Groningen in the Netherlands under the guidance of Professor Hans Wynberg. After working as a research scientist at Shell he was appointed full professor at the University of Groningen in 1988 and named the distinguished Jacobus H. van't Hoff Professor of Molecular Sciences in 2004. He was elected foreign honorary member of the American Academy of Arts and Sciences and member of the Royal Netherlands Academy of Sciences. His research interests include stereochemistry, organic synthesis, asymmetric catalysis, molecular switches and motors, self-assembly and nanosystems.

Moreover, waste salts from zinc and aluminium reagents can be highly toxic.⁵

We present here an overview of the recent literature from 2003 concerning advances in enantioselective copper-catalyzed 1,4-addition including new developments such as trapping reactions, tandem reactions, synthetic applications and mechanistic studies.¹⁵

2. Phosphorus ligands

2.1 Phosphoramidites

Phosphoramidites have shown exceptional selectivity and versatility in conjugate addition in the earlier stages of this development.^{13,14,16} In subsequent years, over 400 new chiral ligands and catalysts were introduced for this asymmetric transformation, several of them reaching high levels of enantioselectivity. In numerous cases phosphoramidites have shown to be the ligands of choice to achieve high enantioselectivity. Notably so also are phosphites and dipeptide-based diarylphosphines, introduced by Alexakis and Hoveyda, respectively; the latter ligands being particularly effective for acyclic (chalcone-type) enones. The early developments and breakthroughs have been extensively reviewed.^{15,16} Mono-dentate phosphoramidite ligands (Fig. 1) showed exceptional versatility in a range of asymmetric transformations including hydrogenations, conjugate additions, allylic substitutions soon after their introduction as privileged chiral ligands. It was shown that they frequently matched stereoselectivities that had so far been the domain of bidentate chiral ligands. Their modular nature allows easy variation of both diol and amine parts and fine tuning of the ligand properties for a specific conversion, as is particularly evident from library approaches in catalyst screening.¹⁷ Binaphthyl-based phosphoramidite ligands in particular have been widely explored.

2.1.1 Organozinc reagents. The initial breakthrough in enantioselective copper-catalyzed asymmetric 1,4-addition

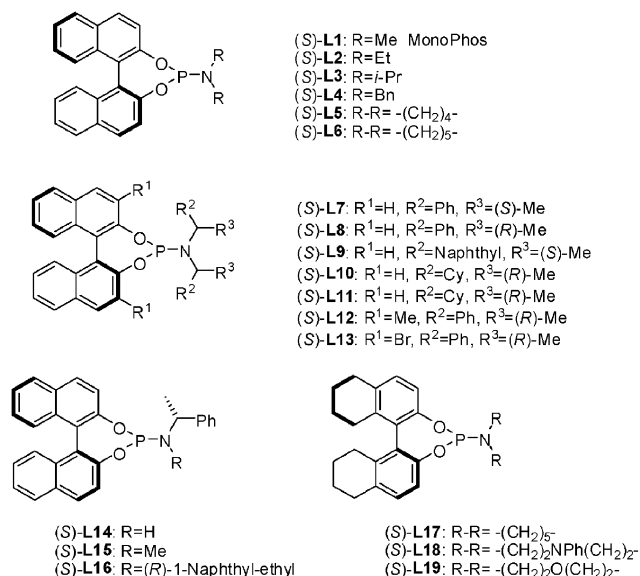


Fig. 1 Chiral binol-based phosphoramidite ligands.

reactions of R₂Zn reagents to cyclic and acyclic enones was achieved using phosphoramidite ligand MonoPhos **L1**, based on a chiral binaphthol and a dimethylamine moiety.¹³ Cyclic enones such as cyclohexenone or acyclic chalcones were the first substrates used in enantioselective copper-catalyzed 1,4-addition of dialkylzincs and then became benchmark substrates. Easy tuning of the aryl or/and amine moieties of the ligand allowed the development of a huge variety of ligands (Fig. 1). Phosphoramidite ligands **L1–L6** were developed at the beginning using achiral amines and the rigid chiral binaphthyl backbone as element of chirality transfer during the enantioselective 1,4-addition. Adding a chiral amine such as (*R,R*)- or (*S,S*)-bis(phenylethyl)amine in the Feringa ligand **L7** allowed the reaching of higher enantioselectivity than MonoPhos **L1**.¹⁴ However, due to the interaction of the chiral binaphthyl backbone and the two stereogenic centres of the amine moiety, matched and mismatched effects were observed during the catalysis. So far, the combination of Cu(I) or Cu(II) salt (reduced *in situ* to Cu(I) by ZnR₂) with monodentate phosphoramidite ligand **L8** gives the best results in the copper-catalyzed 1,4-addition of dialkylzincs to α,β-unsaturated systems.

Other modifications have been achieved in the structure of phosphoramidite ligands on the diol moiety. Chiral biphenol-based ligands **L20–L30** have shown to give somehow the same reactivity compared to binol-based phosphoramidites in the 1,4-addition of dialkylzinc reagents to cyclic and acyclic α,β-unsaturated enones (Fig. 2).

Furthermore, phosphoramidite ligands **L31–L45** based on a racemic and dynamic biphenol moieties and a chiral amine are excellent ligands to induce enantioselectivity in 1,4-addition as demonstrated by Alexakis and co-workers (Fig. 3). Indeed, the atropisomerism of the biphenol part of the ligand is governed by the chiral amine and enantioselectivities in the 1,4-addition

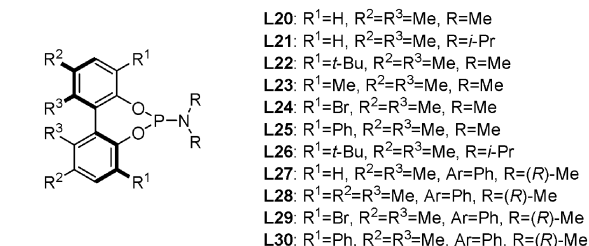


Fig. 2 Chiral biphenol-based phosphoramidite ligands.

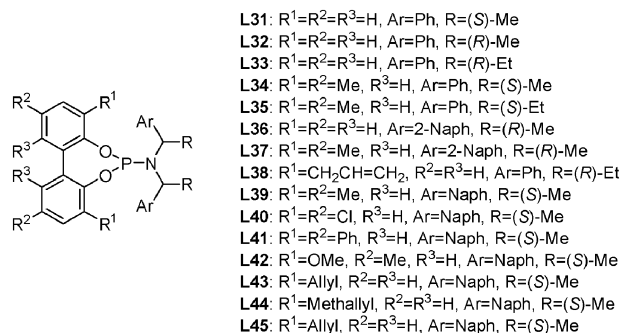


Fig. 3 Racemic biphenol-based phosphoramidite ligands.

of diethylzinc to cyclic and acyclic enones up to 96 and 95% ee, respectively, are readily achieved.¹⁸ Phosphoramidite ligands **L39–L45** possessing a biphenol and a highly bulky bis-(*S*)-(1-naphthalen-2-yl-ethyl)amine allowed the enantioselectivity to be increased in the addition of diethylzinc to cyclic enones (up to 99+ %); however only lower ee values were obtained in the case of acyclic α,β -unsaturated enones.¹⁹

Other chiral diol backbones such as spiro-phosphoramidite ligands **L46–L49**, synthesized from enantiomerically pure 1,1'-spirobiindane-7,7'-diol, showed high efficiency in the conjugate addition of diethylzinc to cyclohexen-1-one and chalcone derivatives (Fig. 4).²⁰ With 3 mol% of $\text{Cu}(\text{OTf})_2$ and 6 mol% of **L46–L50**, in toluene at 0 °C, the 1,4-adduct from cyclohexenone was obtained in high yield and enantioselectivity (up to 99% and 98%, respectively). Lower temperature (–20 °C) was required for the addition to chalcone derivatives, providing products in moderate to good yield (65–89%) and ee (40–76%).

Excellent yields and enantioselectivities (typically in the range 94–99% ee) were obtained in the 1,4-addition of diethylzinc to six and seven-membered cyclic enones in toluene at –20 °C with 3 mol% of CuOAc and 6 mol% of chiral spiro-phosphoramidite ligand **L54** (Fig. 4) based on the rigid unit 9,9'-spirobixanthene-1,1'-diol and chiral amine moieties.²¹ The use of ligands **L51–L53** with non-chiral amines gave the 1,4-addition adduct in only low enantioselectivities (up to 57% ee), indicating the importance of the chiral amine for the chirality transfer.

Taddol has also been used as diol in the synthesis of phosphoramidite ligands (Fig. 5). However only low enantioselectivity was observed in the conjugate addition of diethylzinc to cyclic and acyclic α,β -unsaturated enones (up to 49% ee).²²

Approaches toward immobilisation of phosphoramidite ligands were investigated. In 2003, Waldmann and co-workers reported the preparation of a small library of polystyrene-supported binaphthol-based phosphoramidite ligands containing a piperidine or a bispidine-type amine unit, and their use in the asymmetric conjugate addition of diethylzinc to 2-cyclohexen-1-one (Fig. 6). While this approach allowed the evaluation of the influence of the substitution pattern of the binaphthyl and amine moieties on the enantioselectivity, the ee values did not exceed 67% and recycling of the immobilised ligand **L59** was not described.²³

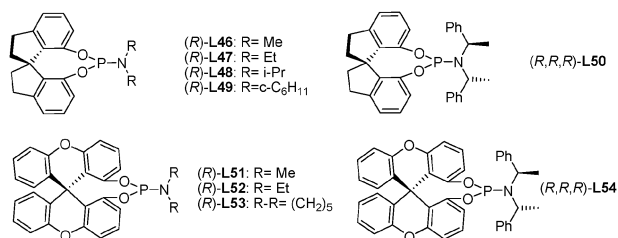


Fig. 4 Spiro-phosphoramidite ligands.

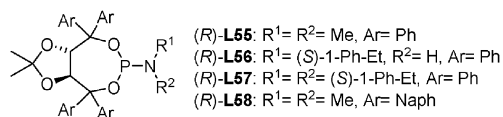


Fig. 5 Taddol-based phosphoramidite ligands.

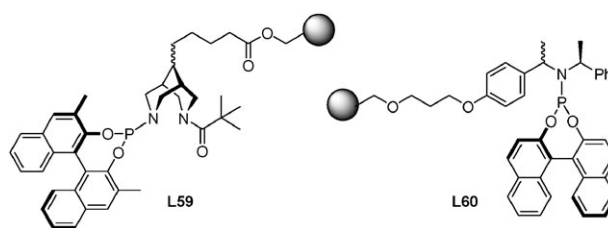
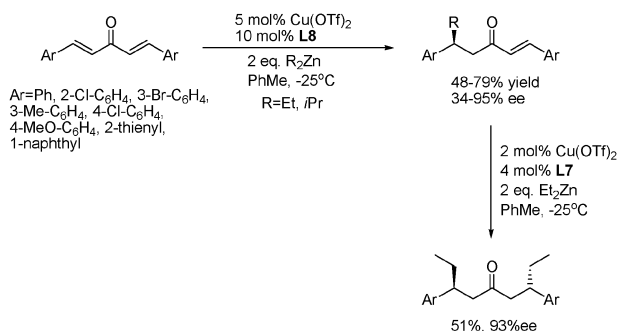


Fig. 6 Immobilized phosphoramidite ligands.

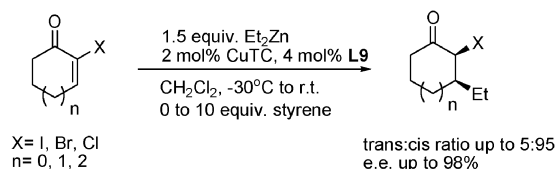
Immobilisation of a library of phosphoramidite ligands was also reported using a Merrifield resin. After screening, the best ligand **L60** (Fig. 6) was used in enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one. Excellent yield and good enantioselectivity were obtained in the first run (respectively, 99% and 84%). The insoluble polymer bound ligand could be simply recovered by filtration, affording complete conversions and ee values in the range of 65–84% in the course of successive runs.²⁴

During the past years, this large library of phosphoramidite ligands **L1–L60** which includes modification of both the diol backbone and the amine moiety, has been shown to be very efficient in the asymmetric copper-catalyzed 1,4-addition of dialkylzinc reagents to cyclic and acyclic enones. Recent investigations allowed the development of the use of a combination of catalytic copper source and phosphoramidite ligand in asymmetric conjugate addition of dialkylzinc to a large variety of substrates, increasing the versatility of this catalytic system. In most of the cases, $\text{Cu}(\text{L8})_2$ has shown excellent conversion and enantioselectivity. Dienone derivatives represent good substrates in the 1,4-addition of dialkylzinc reagents since they can be subjected to two consecutive conjugate addition reactions (Scheme 3).²⁵ After a first addition step of dialkylzinc to dienones in the presence of 5 mol% of $\text{Cu}(\text{OTf})_2$ and 10 mol% of **L8**, 1,4-addition products have been isolated in good to high yield and high enantioselectivity. A subsequent 1,4-addition of diethylzinc to the resulting enone allowed the expected ketone to be obtained with high enantioselectivity (93%). However, the diastereoselectivity was modest since 28% of the achiral *meso*-analogue was obtained as well.

The conjugate addition of diethylzinc to α -halo-cyclohexenones has been recently described by Alexakis and Li using 2 mol% of copper thiophene carboxylate (CuTC) and 4 mol% of phosphoramidite ligand **L9** (Scheme 4). While the enantioselectivities were good (up to 88%), addition of styrene



Scheme 3 Consecutive 1,4-addition of diethylzinc to dienones.



Scheme 4 1,4-Addition of diethylzinc to α -halo-cyclohexenones.

drastically improved the enantioselectivity up to 98%. The effect of styrene was attributed to the fact that it can act as a radical scavenger, preventing an achiral radical pathway.²⁶

Carreira and co-workers investigated the copper-catalyzed asymmetric conjugate addition of diethylzinc to Meldrum's acid derivatives.²⁷ Using 1 to 2 mol% of $\text{Cu}(\text{O}_2\text{CCF}_3)_2$ and three equivalents of monodentate phosphoramidite ligand **L10** in THF at -78°C , 1,4-addition products were obtained in good yields (61–94%) and modest to high enantioselectivities (40–94%). Subsequently, the asymmetric synthesis of all-carbon benzylic quaternary stereocentres was studied by Fillion and Wilsily (Scheme 5).²⁸ With a catalyst based on 5 mol% of $\text{Cu}(\text{OTf})_2$ and 10 mol% of Feringa ligand **L8**, the addition of dialkylzinc to 5-(1-arylalkylidene) Meldrum's acid derivatives allowed quaternary centres to be obtained in high yield and enantioselectivity (up to 99% and 95%, respectively). Using the same reaction conditions, enantiomerically pure 1,1-disubstituted chiral indanes were synthesized quantitatively.

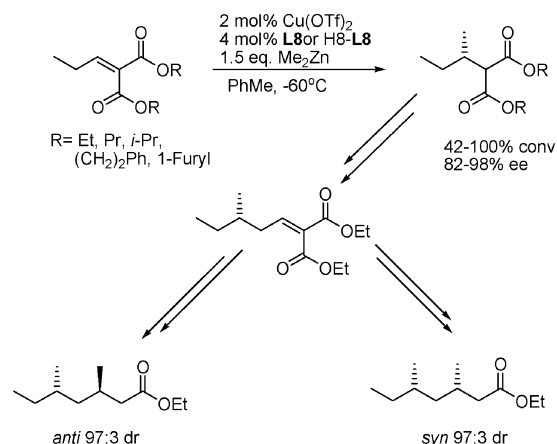
Unsaturated malonic esters were used as substrates in the copper-catalyzed 1,4-addition of dimethylzinc (Scheme 6).²⁹ In toluene at -60°C with 2 mol% of $\text{Cu}(\text{OTf})_2$ and 4 mol% of **L8**, 1,4-adducts were obtained in moderate to excellent conversion and enantioselectivity up to 98%. The configuration of the new stereogenic centre is controlled using **L8** or *ent*-**L8**. A sequence involving reduction of the ester moiety to the corresponding alcohol, oxidation to the aldehyde and subsequent Knoevenagel condensation gave access to unsaturated diesters which could be submitted to a second asymmetric 1,4-addition. This iterative and stereodivergent route allowed the synthesis of *syn* and *anti* 3,5-dimethyl esters with excellent diastereoselectivity as shown in Scheme 6.

In the presence of a low loading of copper source (1.5 mol%) and 3 mol% of **L8**, the conjugate addition of dialkylzinc to α,β -unsaturated lactams bearing appropriate protecting-activating groups on the nitrogen was achieved (Scheme 7).³⁰ β -Alkyl-substituted δ -lactams were synthesized in good yield (up to 70%) and excellent enantioselectivity (up to 95%).

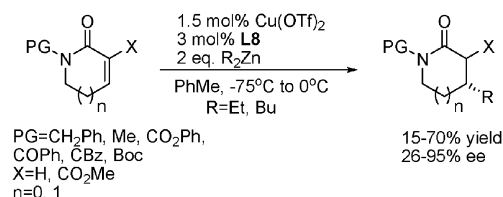
α,β -Unsaturated imines were also investigated in the copper-catalyzed conjugate addition of dialkylzincs. With 10 mol% of CuTC and 10 mol% of **L7** in toluene at room



Scheme 5 1,4-Addition of dialkylzincs to Meldrum's acid derivatives.



Scheme 6 Iterative 1,4-addition of dimethylzinc to α,β -unsaturated malonic esters.

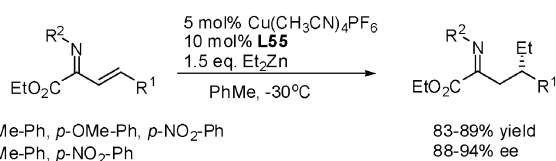


Scheme 7 1,4-Addition of dialkylzinc reagents to α,β -unsaturated lactams.

temperature, the addition of dimethylzinc to 2-pyridylsulfonyl imines of chalcones allowed the desired products to be obtained in high yield and enantioselectivity (up to 90% and 80%, respectively).³¹ The metal-coordinating sulfonyl moiety of the substrate has been shown to be a key element for high chemical yields and enantioselectivities. Addition of diethylzinc to α,β -unsaturated ketimines derived from α -amino acids was reported in the presence of 5 mol% of $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ and 10 mol% of monodentate Taddol-based phosphoramidite ligand **L55** (Scheme 8, Fig. 4).³² Dehydroamino acids with a stereogenic centre at the γ position were synthesized in good yield (up to 89%) and enantioselectivity (94%).

N-Acylpyrrolidinones, as simple derivatives of α,β -unsaturated carboxylic acids, were found to be good substrates in the conjugate addition of dialkylzinc reagents since 1,4-addition products were obtained in high yield and enantioselectivity (up to 99%) in the presence of 1.5 mol% of copper source and 3 mol% of ligand **L8** (Scheme 9).³³

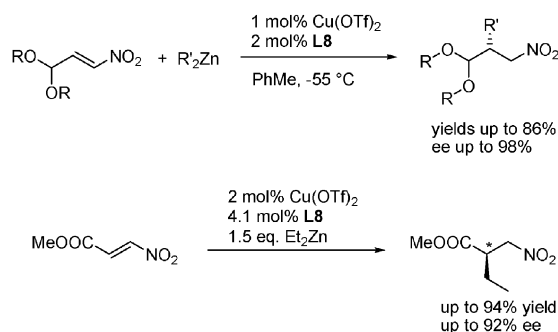
Nitroolefins represent an important class of substrates for the 1,4-addition reaction due to the versatility of the nitro group in organic synthesis. For example, enantioselective 1,4-addition to nitroalkenes provides an attractive route to β^2 -amino acids, which are important building blocks in the



Scheme 8 1,4-Addition of diethylzinc to α,β -unsaturated ketimines.



Scheme 9 1,4-Addition of dialkylzinc reagents to *N*-acylpyrrolidinones.



Scheme 10 1,4-Addition of dialkylzinc to α,β -unsaturated nitrocompounds.



Scheme 11 1,4-Addition of diethylzinc to α,β -unsaturated nitro compounds.

synthesis of natural products, β -peptides and pharmaceuticals.³⁴ The copper-catalyzed addition of organozinc reagents to acetal substituted nitroalkenes was developed by Feringa *et al.*³⁵ Using 1 mol% of $\text{Cu}(\text{OTf})_2$ and 2 mol% of the chiral phosphoramidite **L8**, excellent results were obtained both in terms of yields and enantioselectivities in the conjugate addition of several organozinc reagents to nitroalkenes (Scheme 10). The same catalytic system was used by Sewald in the conjugate addition of diethylzinc to the activated methyl-3-nitropropenoate. The resulting 1,4-adducts were obtained in good yield and enantioselectivity (up to 92% ee).³⁶

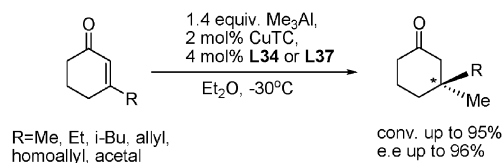
5,5',6,6'-Tetramethylbiphenol-based phosphoramidite ligand **L27** in combination with $\text{Cu}(\text{OTf})_2$ gave good to excellent ee's (67–99%) in the 1,4-addition of diethylzinc to nitroalkenes (Scheme 11).³⁷ Whatever the nature of the aryl, full conversion was obtained. The position of the substituent at the aryl moiety has a huge effect on the enantioselectivity, and *m*- and *o*-substituted aryl moieties gave a lower enantioselectivity compared to *p*-substituted ones.

2.1.2 Organoaluminium reagents. The use of trialkylaluminium as alkylating agents instead of dialkylzinc compounds represent new opportunities in copper-catalysed 1,4-addition. Promising preliminary results in copper-catalyzed conjugate addition of trialkylaluminium to enones has been achieved by Woodward and co-workers using 2-hydroxy-2'-alkylthio-1,1'-binaphthyl ligands.³⁸ Using phosphoramidite ligands, pioneering work was done by Pineschi and co-workers in the copper-catalyzed 1,4-addition of

trialkylaluminium to α,β -unsaturated lactams.³⁰ Due to the higher Lewis acidity of aluminium compared to zinc, faster reactions are expected. Even though the reaction rate was high (full conversion within 2 h), the enantioselectivity was modest (up to 68%) and lower compared to the addition of dialkylzincs (up to 95% ee, Scheme 7). Using a mixture of **L8** and CuTC, Alexakis, Woodward and co-workers showed that the addition of trimethyl- and triethylaluminium to linear and cyclic enones allowed 1,4-addition products with ee's in the range of 86–98% to be obtained.³⁹ After 20 min, products were isolated in good yield (up to 90%). This protocol allowed the first enantioselective addition of vinylalane to cyclic enones to afford the (+)-stereoisomer with good enantioselectivity (up to 77%). Due to the enhanced Lewis acidity of aluminium, compared to zinc, the addition to the more sterically hindered trisubstituted enones proceeds as well. Using 2 mol% of CuTC and 4 mol% of phosphoramidite ligand **L34** or **L37** based on a racemic diphenyl moiety, Alexakis and co-workers developed the first asymmetric catalytic conjugate addition to trisubstituted cyclohexenones creating stereogenic quaternary centres in excellent yields and enantioselectivities (Scheme 12).⁴⁰ Further investigations allowed the 1,4-addition of trialkylaluminium reagents to a broad class of trisubstituted cyclic enones to be performed in good yields and enantioselectivities.⁴¹

Changing the rigid biphenol backbone of the phosphoramidite ligand **L27** to the more flexible structures **L61–L62** resulted in lower enantioselectivity (up to 35% ee) in the copper catalyzed 1,4-addition of diethylzinc to cyclohexanone. The use of **L63** provided 95% ee in the same reaction (Fig. 7); the higher enantioselectivity might be induced by the more important atropomorphism effect on the diphenylphosphine moieties due to its proximity with the chiral amine.⁴²

L63 has also been shown to be efficient in the addition of trialkylaluminium to β -substituted cyclohexenones since 1,4-addition products possessing a quaternary stereogenic centre were obtained in high yields and ee up to 93% (Scheme 13).



Scheme 12 Creation of quaternary stereogenic centre from the addition of trimethylaluminium to trisubstituted cyclohexenones.

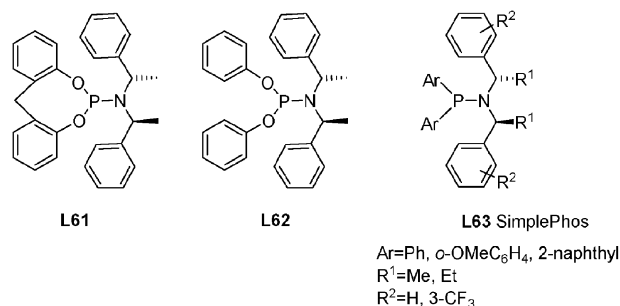
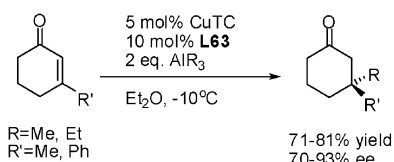


Fig. 7 Flexible phosphoramidite and SimplePhos ligands.



Scheme 13 1,4-Addition of trimethyl- and triphenylaluminum to substituted cyclohexenones.



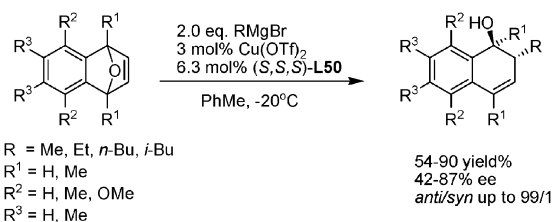
Scheme 14 1,4-Addition of trimethylaluminum to α,β -unsaturated nitroalkenes.

Trimethylaluminum could also replace dimethylzinc in the copper-catalyzed conjugate addition to a wide variety of α,β -unsaturated nitroalkenes. Using 2 mol% of CuTC and 4 mol% of **L38** in diethyl ether at $-30\text{ }^{\circ}\text{C}$, yields up to 77% and enantioselectivities up to 93% were reached (Scheme 14).⁴³

2.1.3 Organomagnesium reagents. Up to now, only one example using phosphoramidite ligands in the copper-catalyzed conjugate addition of Grignard reagents has been reported.⁴⁴ Ring-opening reactions of oxabenzonorbornadiene derivatives using chiral spiro-phosphoramidite ligand **L50** (Fig. 4) afforded the desired product with excellent diastereoselectivity (*anti/syn* up to 99/1) and modest to good yield and enantioselectivity (up to 87% ee), (Scheme 15).

2.2 Phosphines

2.2.1 Ferrocene-based phosphine ligands. In 2004, Feringa and co-workers reported the use of ferrocenyl-based diphosphine ligands such as Taniaphos **L64**, Josiphos **L65** and related ligands (Fig. 8) in combination with CuCl or CuBr·SMe₂ in the copper-catalyzed 1,4-addition of Grignard reagents to cyclic enones. This allowed them for the first time to reach high regioselectivities and unprecedented



Scheme 15 Ring-opening of oxabenzonorbornadiene derivatives.

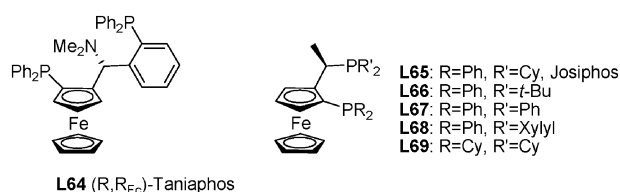
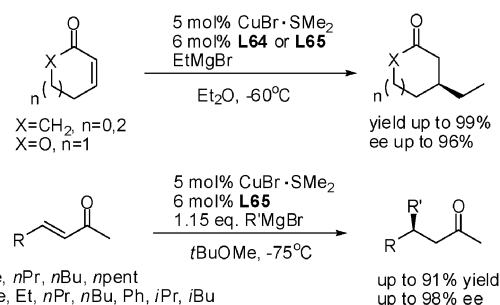


Fig. 8 Ferrocenyl-based diphosphine ligands.

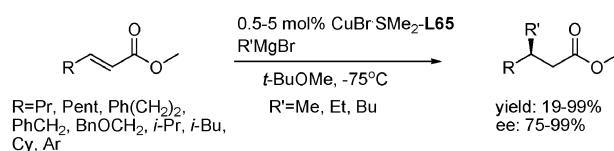


Scheme 16 1,4-Addition of Grignard reagents to acyclic and cyclic α,β -unsaturated carbonyl derivatives using ferrocenyl-based chiral ligands.

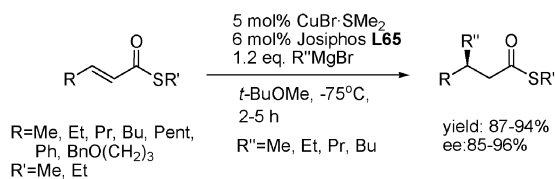
enantioselectivities (up to 96%) (Scheme 16).⁴⁵ Using the same reaction conditions, this breakthrough in asymmetric conjugate addition was exploited in the addition of a broad range of organomagnesium reagents to acyclic α,β -unsaturated ketones, providing 1,4-addition products in high yields and excellent regio- (up to 99 : 1) and enantioselectivities (up to 98%).⁴⁶

In order to increase the substrate scope, and noting the synthetic versatility of chiral esters, investigations on asymmetric conjugate addition to less reactive (compared to enones) α,β -unsaturated esters were developed. The addition of Grignard reagents, Josiphos ligand **L65** (0.6–3.0 mol%) and CuBr·SMe₂ (0.5–2.5 mol%) in *t*-BuOMe at $-75\text{ }^{\circ}\text{C}$ afforded β -substituted esters with excellent enantioselectivities (up to 99% ee) (Scheme 17).⁴⁷ A broad range of cyclic or acyclic unsaturated esters with different groups at the γ -position participated successfully in the enantioselective conjugate addition. Using acyclic substrates, 1,4-addition products were obtained in good to excellent yields (75–99%) and enantioselectivities (up to 99%). For β -aryl- α,β -unsaturated esters, the method proved to be particularly effective and afforded exclusively the desired 1,4-addition products with enantioselectivities ranging from 88–98% and complete conversion within 3–5 h.

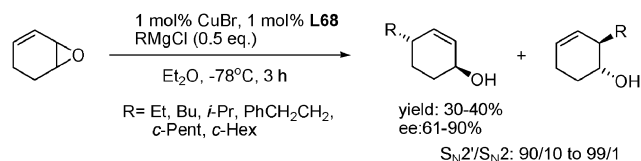
Unfortunately, due to the lower reactivity of methyl Grignards, the highly desired addition of MeMgBr to α,β -unsaturated esters failed. As methyl-branched acyclic units such as deoxypropionates are prominent structural features in numerous natural products, a solution to this problem was found in the use of α,β -unsaturated thioesters. The reduced electron delocalization in the thioester moiety, compared to oxoesters, results in higher reactivity towards conjugate addition reactions. Moreover, the presence of the thioester moiety in the chiral product offers additional synthetic versatility (*vide infra*). The enhanced reactivity of the thioesters allowed the development of a practical method for the addition of methyl Grignard reagents (yields and ee's up to 94% and 96%, respectively) in *tert*-butyl methyl ether at $-75\text{ }^{\circ}\text{C}$, (Scheme 18).⁴⁸ Recently this was used in highly efficient and enantioselective iterative catalytic protocols for the synthesis



Scheme 17 1,4-Addition of Grignard reagents to α,β -unsaturated esters.



Scheme 18 1,4-Addition of Grignard reagents to α,β -unsaturated thioesters.



Scheme 19 Kinetic resolution of 1,3-cyclohexadiene monoepoxide.

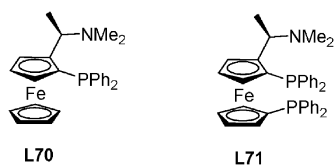


Fig. 9 Bidentate *N,P*-ferrocenyl ligands.

of *syn*- and *anti*-1,3-dimethyl arrays allowing the synthesis of mycroceroic and phthioceroic acid, being tetra- and heptamethyl-branched acids, respectively, from *Mycobacterium tuberculosis* (*vide supra*).⁴⁹

Kinetic resolution of 1,3-cyclohexadiene monoepoxide was developed by Millet and Alexakis using a combination of chiral ferrocenyl-based diphosphine **L68** and CuBr (1 mol%). Moderate to good enantioselectivities (up to 90% ee and 40% yield) and good to excellent regioselectivities (up to 99 : 1) were obtained with various Grignard reagents in diethyl ether at $-78\text{ }^{\circ}\text{C}$ in 3 h, the ring opening reaction most probably proceeding through an anti- $\text{S}_{\text{N}}2'$ pathway (Scheme 19).⁵⁰

The use of bidentate *N,P*-ferrocenyl ligands **L70** and **L71** in copper-catalyzed 1,4-addition of diethylzinc to chalcone gave only low to modest enantioselectivities (up to 41% ee) under mild conditions (Fig. 9).⁵¹ It was found that chalcones bearing *ortho*-substituents led to a dramatic improvement of the enantioselectivity (up to 92% ee).

2.2.2 Binap-based phosphine ligands. Only three examples of copper-catalyzed 1,4-addition of Grignard reagents were reported so far using Binap-type phosphine ligands. Using a combination of 1 mol% of CuI and 1.5 mol% of Tol-Binap **L72** (Fig. 10), Loh and co-workers described the conjugate addition of a broad range of Grignard reagents (secondary, bulky and unsaturated) to (*E*)-methyl-5-phenylpent-2-enoate in *t*-BuOMe at $-40\text{ }^{\circ}\text{C}$, affording highly enantioenriched β -substituted esters (86–94% ee) in good yields (86–91%).⁵²

The same methodology has been used in the 1,4-addition of ethylmagnesium bromide to different α,β -unsaturated esters in good yields (80–90%) and enantiomeric excess (70–95%) (Scheme 20). The addition of methylmagnesium bromide resulted in enantiomeric pure product ($>98\%$ ee) albeit only in 20% yield, due to the major formation of 1,2-addition product.⁵² Further investigations allowed the addition of

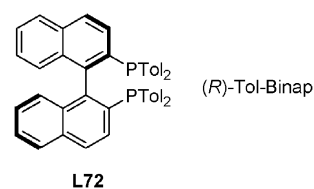
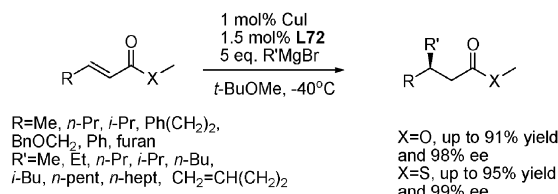


Fig. 10 Binap-type ligand.



Scheme 20 1,4-Addition of Grignard reagents to α,β -unsaturated esters and thioesters.

methylmagnesium bromide to a broad range of α,β -unsaturated esters by increasing the temperature to $-20\text{ }^{\circ}\text{C}$.⁵² It was found that the absolute stereochemistry of the product can be reversed either by using the other enantiomer of the ligand or by using the geometrical isomer of the starting material.

Using the same reaction conditions at $-70\text{ }^{\circ}\text{C}$, the highly efficient conjugate addition of methylmagnesium bromide to a broad range of more reactive aromatic and aliphatic α,β -unsaturated thioesters allowed to obtain 1,4-addition adducts in excellent yield and enantioselectivity (up to 95% and 99%, respectively) (Scheme 20).⁵³

2.2.3 Amino acid-based phosphine ligands. Hoveyda developed an easily accessible library of amino acid-based phosphine bidentate ligands and used them for the conjugate addition of dialkylzincs to α,β -unsaturated enones (Fig. 11). A combination of $(\text{CuOtf})_2\cdot\text{C}_6\text{H}_6$ and peptidic phosphine **L75** in the 1,4-addition to five-, six-, and seven-membered ring cyclic enones gave 1,4-addition products in high yields and very high ee's (up to 98%).⁵⁴ This catalytic system also showed excellent results with acyclic aliphatic enones, giving yields and enantioselectivities up to 90% and 95%, respectively.⁵⁵

The library of amino acid based phosphine ligands was also screened in the addition of dialkylzincs to aliphatic substituted *N*-acyloxazolidinones, affording 1,4-adducts in moderate to good yields (61–95%) and enantioselectivities up to 98% using **L78** (Scheme 21).⁵⁶ Low reactivity was observed with phenyl-substituted *N*-acyloxazolidinones. Functionalization of the oxazolidinone ring with methyl groups allowed the synthesis of the 1,4-addition product in good yield and enantioselectivity (91% and 86%, respectively). Enriched β -alkyl-*N*-acyloxazolidinones were then converted with complete retention of stereochemistry into carbonyl derivatives that were not accessible through direct asymmetric catalytic 1,4-addition reactions of organozinc reagents.

Using **L76**, 1,4-addition of dimethyl- and diethylzinc to aliphatic acyclic nitroalkenes afforded the addition adduct with modest yields and good to excellent enantioselectivities (up to 95%).⁵⁷ This methodology was extended using amino acid-based chiral phosphine ligands **L76** and **L80** in the conjugate addition of dialkylzincs to small-, medium-, and

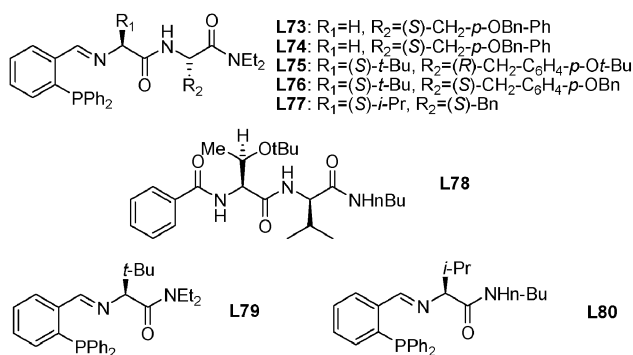
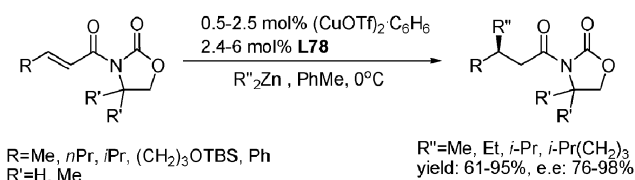


Fig. 11 Amino acid-based phosphine bidentate ligands.



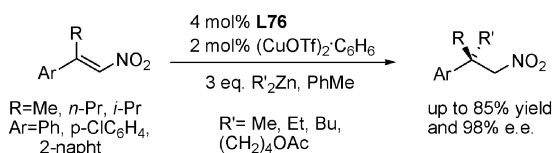
Scheme 21 1,4-Addition of dialkylzinc to aliphatic substituted *N*-acyloxazolidinones.

large-ring nitroolefins with excellent conversions and enantioselectivities (up to 96%).⁵⁸ All 1,4-addition products were found to be *syn*, and could be easily converted to the *anti* diastereoisomer without lowering of the enantiomeric excess. Particularly noteworthy is the enantioselective synthesis of nitroalkanes bearing all-carbon quaternary stereogenic centres through copper-catalyzed asymmetric conjugate additions to trisubstituted nitroalkenes using 2 mol% of $(\text{CuOTf})_2\cdot\text{C}_6\text{H}_6$ and 4 mol% of ligand **L76** in toluene (Scheme 22).⁵⁹ The resulting nitroalkanes (ee up to 98%) are suitable precursors to synthetically versatile chiral synthons, such as amines, nitriles, aldoximes, and carboxylic acids.

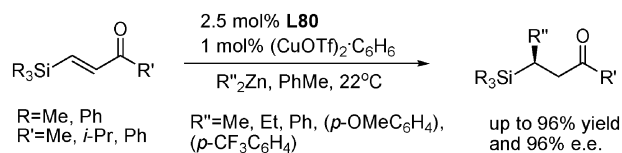
The readily available and simple valine-based chiral phosphine **L80** was recently used to promote highly efficient catalytic asymmetric conjugate additions of dialkyl- and diarylzinc reagents to acyclic β -silyl- α,β -unsaturated ketones (Scheme 23).⁶⁰ The catalytic asymmetric protocol allowed access to versatile trisubstituted allylsilanes with high diastereomeric (20 : 1) and enantiomeric excess (96% ee).

Highly enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one has been described recently by Tomioka *et al.*, using 5 mol% of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ and a slight excess of peptidic amidomonophosphane ligand **L81** in toluene at 0 °C (Fig. 12).⁶¹ The 1,4-addition product was obtained after 2 h in 87% yield and high ee (98%). Other diorganozinc reagents, including functionalized ones, gave the corresponding substituted cyclohexanones with 45–94% ee but required longer reaction times.

Catalytic kinetic resolution procedures for 5-substituted cycloalkenones with excellent enantioselectivities were



Scheme 22 1,4-Addition of dialkylzinc to trisubstituted nitroalkenes.



Scheme 23 1,4-Addition of dialkyl- and diarylzinc to acyclic β -silyl- α,β -unsaturated ketones.

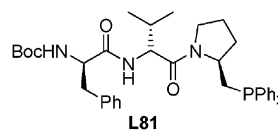


Fig. 12 Peptidic amidomonophosphane ligand.

developed earlier using a copper–phosphoramidite catalyst.⁶² The catalytic system based on **L81** has recently also been applied in the kinetic resolution of 5-substituted cyclohexenones by copper-catalyzed asymmetric conjugate addition of diethylzinc (Scheme 24).⁶³ Enantioenriched 5-substituted cyclohexenones were recovered (88–98% ee and 28–41% yield) along *trans*-3-alkylated 5-substituted cyclohexanones (53–60% yield and 81–90% ee).

Asymmetric conjugate addition of diethylzinc to β -aryl- α,β -unsaturated *N*-2,4,6-trisopropylphenylsulfonylaldimines was achieved using 5 mol% of *N*-Boc-L-Val-modified amidophosphane **L82** and $\text{Cu}(\text{MeCN})_4\text{BF}_4$ in toluene at –30 °C (Fig. 13). After hydrolysis of the imine to the aldehyde through the use of aluminium oxide and reduction with sodium borohydride, the corresponding β -alkylated alkanols were obtained in good yields and enantioselectivities in the range of 67% to 91% (Scheme 25).⁶⁴

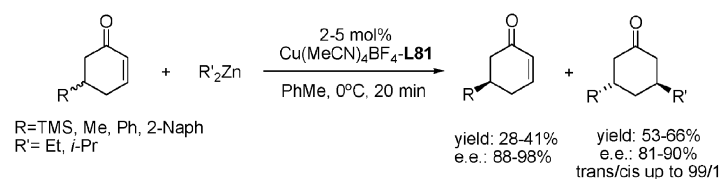
The related proline-based ligand **L83** was also used in 1,4-addition of dialkylzinc to β -aryl- and β -alkylnitroalkenes (Scheme 26).⁶⁵ With 5 mol% of $\text{Cu}(\text{OTf})_2$ and 6 mol% of ligand **L83**, 1,4-addition products were obtained in moderate yield and enantioselectivity (up to 67% and 80%, respectively).

The use of valine and proline-based ligands **L84–L86** in combination with $\text{Cu}(\text{OTf})_2$ in dichloromethane allowed the 1,4-addition of diethylzinc to six- and seven membered cyclic α,β -unsaturated enones in good yield (75–92%) and enantioselectivity (up to 87% ee) (Fig. 14).⁶⁶ Conjugate addition of diethylzinc to chalcone gave ee's up to 81%.

2.2.4 Mixed phosphine ligands. Chiral bicyclic P,O ligands **L87–L88** have been evaluated in the conjugate addition of butylmagnesium chloride to 2-cyclohex-1-one (Fig. 15). Modest yields, enantioselectivities and low regioselectivity were obtained.⁶⁷

Bidentate P-chiral phosphinophenol **L89** and phosphinoanisole **L90** ligands were used as P,O hybrid ligands in the conjugate addition of diethylzinc to chalcone derivatives (Fig. 16).⁶⁸ In diethyl ether at 0 °C using 1 mol% of $\text{Cu}(\text{OTf})_2$ and a slight excess of ligand, reactions proceeded smoothly and were complete within 0.3–1.5 h, giving the addition products in high to excellent yields (up to 98%) and high enantioselectivities (up to 96%).

The hemilabile heterobidentate chiral Binapo **L91** gave good to high enantioselectivities (up to 91%) in the addition



Scheme 24 Kinetic resolution of 5-substituted cyclohexenones.

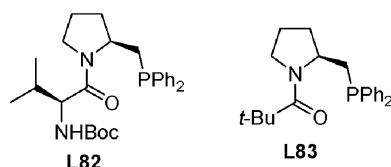


Fig. 13 *N*-Boc-L-Val-Modified amidophosphane ligands.

of trialkylaluminum to cyclic and aliphatic acyclic α,β -unsaturated enone derivatives.⁶⁹ Extension of this catalytic system using 3-methyl cyclohexenone and triethylaluminum at -25°C in diethyl ether resulted in the generation of a quaternary stereocentre (86% ee) (Scheme 27).

Other binaphthyl-based ligands such as phosphine-sulfonamide ligand **L92** showed also good results in conjugate addition reactions (Fig. 17).⁷⁰ Applied to 1,4-addition of diethylzinc to acyclic enones such as benzylideneacetone and derivatives, very high enantioselectivities were observed (up to 99% ee). Excellent results were also obtained with chalcones and acyclic aliphatic enones using 1 mol% of $\text{Cu}(\text{OTf})_2$ and a slight excess of phosphino-phenol ligands **L93–L97**.⁷¹ Within this family of ligands, a negative non-linear effect between the ee of the product and the ee of the ligand was observed, indicating that the copper ion and the ligand form preferentially a *meso*-2 : 1 ligand–Cu complex. The use of 2 mol% of the tridentate dimethylaminoethoxyphosphine ligand **L98**, in combination with 1 mol% of $\text{Cu}(\text{OTf})_2$ in the addition of diethylzinc to 2-cyclohexen-1-one afforded under optimized reaction conditions the 1,4-addition adduct in quantitative yield and 99% ee (Fig. 17).⁷²

Krauss and Leighton introduced phosphine-sulfonamide ligand **L99** for the copper-catalyzed conjugate addition of dialkylzinc to cyclic enones. In the presence of 2 mol% of $\text{Cu}(\text{OTf})_2$ in dichloromethane, yields up to 90% and good to excellent enantioselectivities (up to 97%) were obtained (Fig. 18).⁷³ Interestingly, this ligand provided the highest enantioselectivities at room temperature where as in most previous cases low temperatures were required (*vide supra*).

Reaction of chiral cycloheptenone with diethylzinc catalyzed by $\text{Cu}(\text{OTf})_2$ in the presence of **L99** led to the formation of the *cis*-adduct in 69% yield and 97 : 3 dr (Scheme 28).

P-Chiral phosphine bis(sulfonamide) ligand **L100** was developed for the 1,4-addition of diethylzinc to acyclic enones



Scheme 26 Addition of dialkylzincs to β -aryl- and β -alkylnitroalkenes.

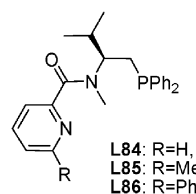


Fig. 14 Amino acid-derived phosphine ligands.

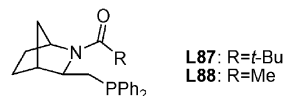


Fig. 15 Chiral bicyclic ligands.

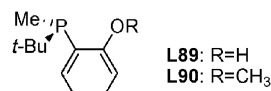
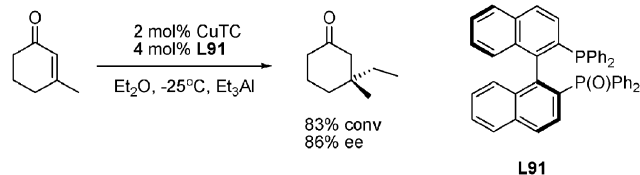
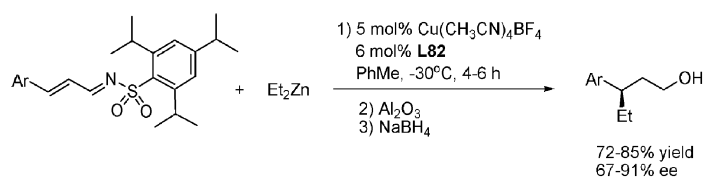


Fig. 16 Bidentate P-stereogenic phosphinophenol ligands.



Scheme 27 Addition of triethylaluminum to 3-methyl cyclohexenone using Binapo ligand.

(Fig. 18). The reactions proceeded with excellent enantioselectivities (up to 95%) with a wide range of acyclic enone substrates, again providing the best results at room temperature.⁷⁴



Scheme 25 Synthesis of β -alkylated alkanols from addition of diethylzinc to β -aryl- α,β -unsaturated *N*-2,4,6-triisopropylphenylsulfonylaldimines.

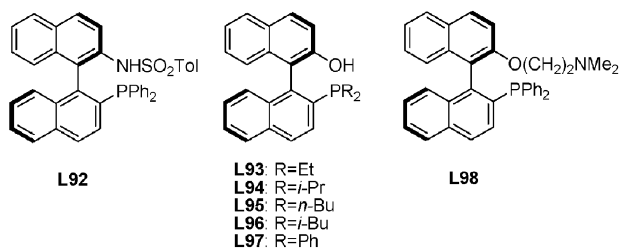


Fig. 17 Phosphine-sulfonamide and phosphino-phenol ligands.

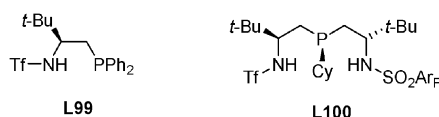
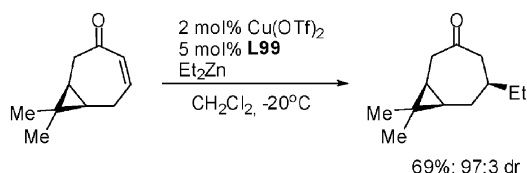


Fig. 18 Phosphine-sulfonamide ligands.



Scheme 28 1,4-Addition of diethylzinc to chiral cycloheptenone.

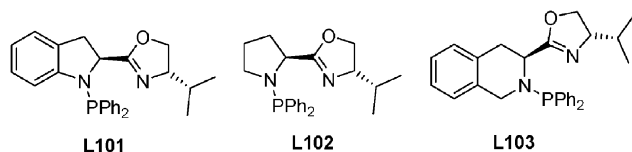


Fig. 19 Aminophosphine-oxazoline ligands.

Furthermore chiral aminophosphine-oxazolines have been applied in the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexen-1-one and chalcone (Fig. 19). Ee's up to 67% with cyclic enone and up to 30% ee with chalcone were obtained with ligand **L101**, based on L-indoline carboxylic acid and L-valinol.⁷⁵

2.3 Phosphites

Early studies on the copper-catalyzed 1,4-addition of diethylzinc to cyclohexen-2-one were carried out by Alexakis in 1997 using phosphite ligands derived from tartrate.⁷⁶

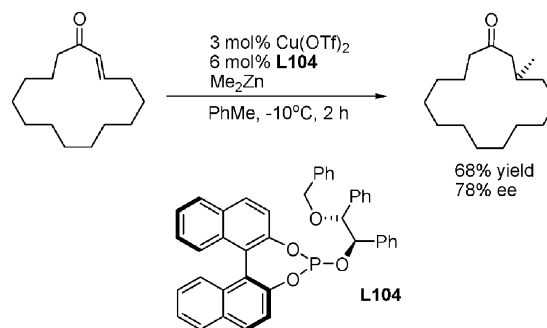
In 2003 an asymmetric synthesis of (*R*)-(-)-muscone, the key odour component of musk, was achieved using the

conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one.⁷⁷ The use of phosphite **L104** as chiral ligand in combination with $\text{Cu}(\text{OTf})_2$ as copper source afforded the desired product in 68% yield and 78% ee (Scheme 29).

Monophosphite ligands containing binaphthol and (*R,R*)-1,2-diphenylethane-1,2-diol were used in the 1,4-addition of dialkylzinc to linear and cyclic α,β -unsaturated enones, but only low ee's were obtained with chalcone as substrate ($\leq 48\%$). Moderate to good enantioselectivity was obtained in the addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one ($\leq 78\%$ ee).⁷⁸

The 1,4-addition of dialkylzinc reagents to acyclic enones with deoxycholic acid-based phosphite ligands **L105** and **L106** gave only moderate enantioselectivities (up to 78%) (Fig. 20).⁷⁹ When applied to the conjugate addition of cyclic enones such as 2-cyclohexen-1-one and (*E*)-cyclopentadec-2-enone, these ligands gave only ee's up to 63%.

Up to now, monodentate phosphite ligands have provided only moderate to good enantioselectivities in the copper-catalyzed conjugate addition of organozinc reagents to α,β -unsaturated enones. Chan *et al.* developed chiral bidentate diphosphite ligands derived from binaphthol **L107** and H_8 -binaphthol **L108**, **L109** and obtained high enantioselectivities (up to 98%) in the 1,4-addition of diethylzinc to cyclic enones (Fig. 21).⁸⁰ As noted before, a decrease of reactivity is seen in the addition of dimethylzinc to 2-cyclopenten-1-one affording product with low enantioselectivity. However, larger ring analogues showed substantially higher reactivity leading to the alkylated product in high yield and excellent enantioselectivity (up to 99% ee). The use of trimethylaluminum in the 1,4-addition to 2-cyclohexen-1-one using diphosphite ligand **L109** was also investigated and ee's up to 96% were obtained.⁸¹ Diphosphite **L110** derived from 3,3',5,5'-tetra-*tert*-butyl-2,2'-biphenol was effective in



Scheme 29 Muscone synthesis using phosphite ligand.

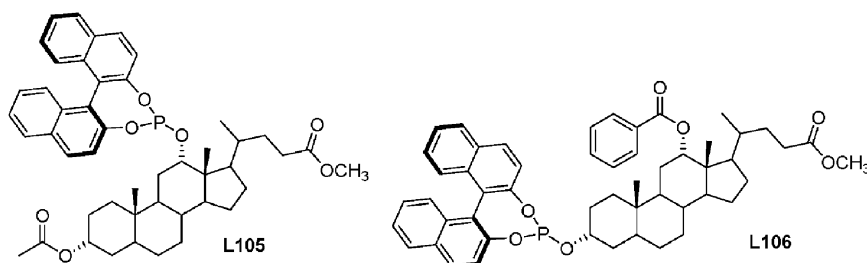


Fig. 20 Monodentate deoxycholic acid-based phosphite ligands.

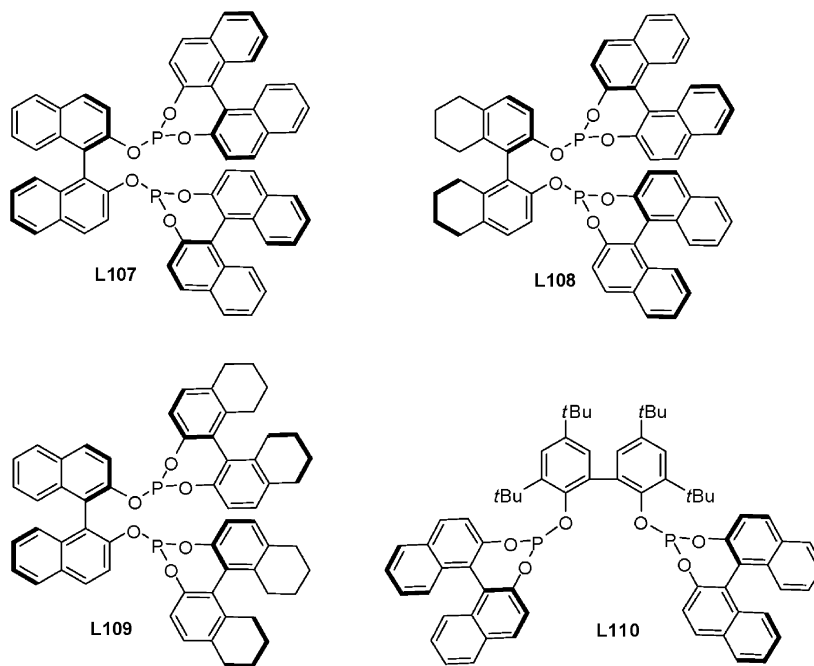


Fig. 21 Binol-based diphosphite ligands.

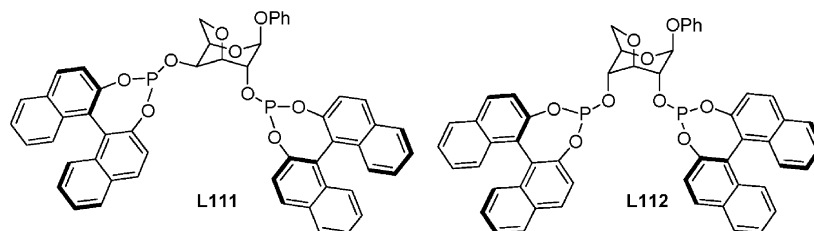


Fig. 22 Pyranoside-based diphosphite ligands.

the 1,4-addition of triethylaluminium to 2-cyclopenten-1-one, affording the product in 92% yield and 94% ee.⁸² Diphosphite ligand **107** also showed high selectivity in 1,4-addition of dialkylzinc to α,β -unsaturated lactones, with ee's up to 98%.⁸³

Diphosphite ligands **L111–L112** featuring pyranoside backbones derived from glucose and galactose, gave good enantioselectivities (up to 88%) in the copper-catalyzed 1,4-addition of diethylzinc to cyclic enones (Fig. 22).⁸⁴ The stereoselectivity was found to be dependent on the ring size of the substrate. While the sense of enantioselectivity is mainly controlled by the configuration of the binaphthyl moieties, the selectivity itself depends on the absolute configuration of the C-4 stereogenic centre of the pyranoside backbone.

Finally, in the presence of 1 mol% of $\text{Cu}(\text{OTf})_2$ and 2 mol% of bidentate diphosphite ligand **L113** based on 1,2;5,6-di-*O*-cyclohexylidene-*D*-mannitol only a moderate enantioselectivity (up to 71%) was obtained in the conjugate addition of diethylzinc to cyclic enones (Fig. 23).⁸⁵

2.4 Miscellaneous ligands

An alanine-derived aminoalcohol-phosphine ligand **L114** was developed by Nakamura for the 1,4-addition of organozinc reagents to α,β -unsaturated acyclic and cyclic enones, giving

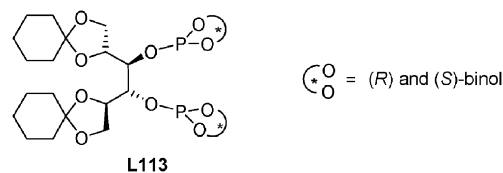


Fig. 23 1,2;5,6-Di-*O*-cyclohexylidene-*D*-mannitol based bidentate diphosphite ligand.

good to excellent enantioselectivities (82–99%) when using 3 mol% of $\text{Cu}(\text{OTf})_2$ and a slight excess of ligand in dichloromethane at 0 °C (Fig. 24).⁸⁶

With 6 mol% of binaphthylphosphorus-thioamidite ligands **L115–L116** and 3 mol% of $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$, addition of diethylzinc to cyclic α,β -unsaturated cyclic enones in toluene afforded high yields in 30 min at 20 °C and excellent enantioselectivities (up to 98%) (Fig. 25).⁸⁷ Other substrates, such as chalcone derivatives ($\leq 97\%$ ee) and acyclic aliphatic enones ($\leq 93\%$ ee) gave also high selectivities. The presence of the sulfur atom in the ligand was found to be crucial to reach high efficiency, due to its strong coordination to Cu(I). To confirm the enhanced reactivity, binaphthylphosphorselenoamidite ligand **L117**, possessing a selenium atom (high affinity for copper(I)) was tested in the 1,4-addition of diethylzinc to

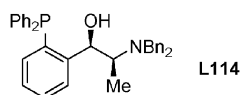


Fig. 24 Alanine-derived aminoalcohol-phosphine ligand.

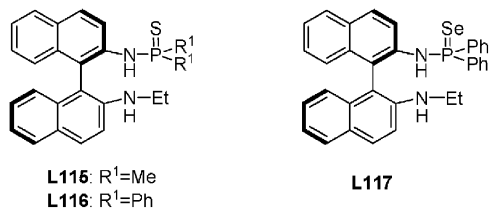


Fig. 25 Binaphthylphosphorus-thioamide ligands.

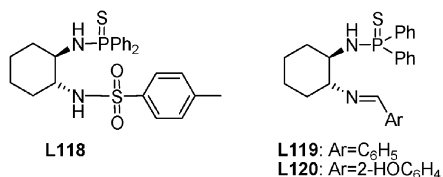


Fig. 26 Sulfonamide-phosphorus-thioamide and imino-phosphorus-thioamide ligands.

five-, six- and seven-membered cyclic enones in toluene at 20 °C affording after 20 min 60–94% yield with ee's in the range 90–93%.

Sulfonamide-phosphorus-thioamide ligand **L118** was used to promote 1,4-addition of diethylzinc to cyclic enones (Fig. 26). In combination of 3 mol% of $\text{Cu}(\text{CH}_3\text{CN})_4\text{ClO}_4$, 6 mol% of **L118** and 10 mol% of LiCl as an additive in diethyl ether at room temperature and 2-cyclopenten-1-one, 2-cyclohexen-1-one and 2-cyclohepten-1-one as substrates, 1,4-addition products were obtained with 47%, 90%, and 73% ee, respectively. It was shown that this ligand was stable and can be recycled and reused in another run without any loss of enantioselectivity.⁸⁸

In the presence of 6 mol% of imino-phosphorus-thioamide ligands **L119** and **L120** and 3 mol% of $\text{Cu}(\text{CH}_3\text{CN})_4\text{ClO}_4$ in toluene at –20 °C, asymmetric addition of diethylzinc to cyclic α,β -unsaturated ketones was achieved in good yields and moderate enantioselectivities (75% ee). The catalytic system was limited to cyclic enones since only racemic 1,4-addition product was obtained in the addition of diethylzinc to chalcone. Using the corresponding imino-phosphorselenoamide ligand, 2-ethylcyclohexanone was obtained in quantitative yield and 62% ee.⁸⁹

Bidentate amino-phosphoramidite ligands **L121–L124**, derived from (*R,R*)-diaminocyclohexane were also tested in the conjugate addition of diethylzinc to 2-cyclohexen-1-one (Fig. 27). The highest enantioselectivity (74% ee) was reached with the *N,N'*-dimethyl substituted P,N-ligand **L121** and $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$.⁹⁰

Mixed chiral phosphoramidite-phosphite ligands **L125** and **L126**, based on binol or H_8 -binol and tropane backbones, were used in copper-catalyzed conjugate addition of diethylzinc to five-, six-, seven- and eight-membered cyclic enones in toluene at –20 °C with 1 mol% of $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ leading to

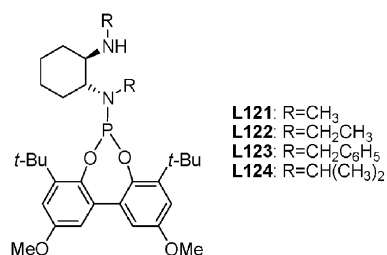


Fig. 27 Bidentate amino-phosphoramidite ligands.

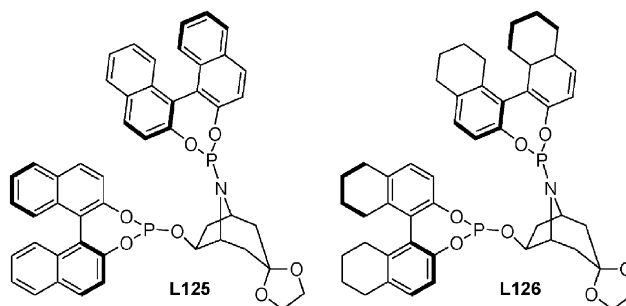


Fig. 28 Chiral phosphoramidite-phosphite ligands.

good ee's (up to 90%) (Fig. 28).⁹¹ An important matched/mismatched effect was observed for this class of ligands since 87% ee was obtained in the addition of diethylzinc to cyclopentenone using (*S,S*)-**L125** and only 5% ee was obtained using (*R,R*)-**L125**. Note that (*S,S*)-**L125** and (*R,R*)-**L125** are diastereoisomeric ligands. Only modest enantioselectivities were obtained with aliphatic acyclic α,β -unsaturated ketones and chalcone derivatives (up to 57% ee).

Hu *et al.* reported asymmetric conjugate addition of diethylzinc to various chalcone derivatives using a combination of 1 mol% of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$ and 2 equiv. of P,N phosphite-pyridine ligands **L127**, **L128** derived from a chiral nobin backbone (2-amino-2'-hydroxy-1,1'-binaphthyl) in toluene at –10 °C with good yields (48–82%) and excellent

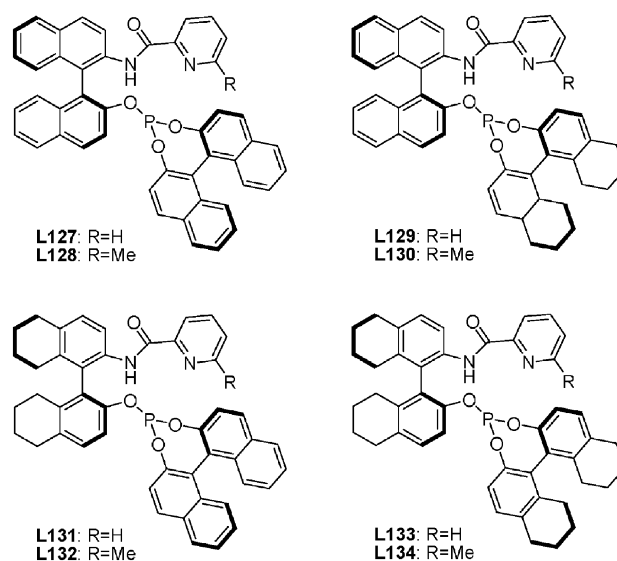


Fig. 29 Phosphite-pyridine ligands.

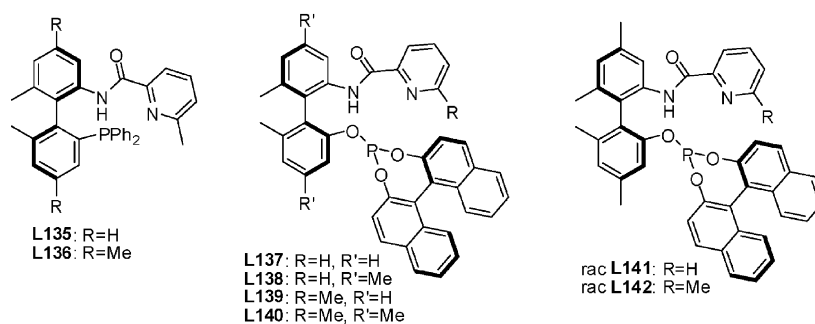


Fig. 30 Chiral-based biphenyl phosphine and phosphite ligands.

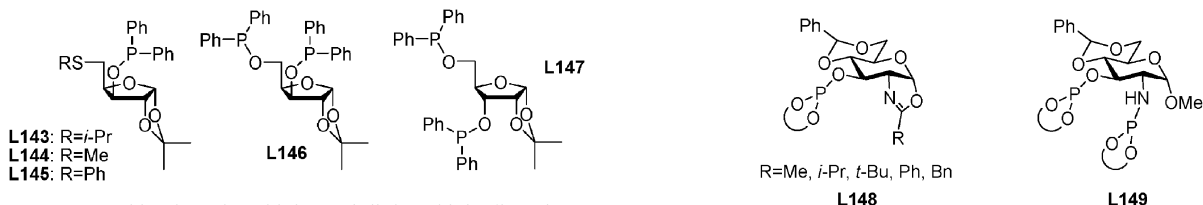


Fig. 31 Thioether-phosphinite and diphosphinite ligands.

enantioselectivities (up to 97%) (Fig. 29).⁹² This catalytic system gave lower ee's ($\leq 53\%$ ee) in the conjugate addition to 2-cyclohexenone. A library of ligands, synthesized from H₈-nobin and/or H₈-phosphite **L129–L134**, was evaluated in the 1,4-addition of diethylzinc to chalcone derivatives achieving good yields and ee's up to 97%.

Ligands based on chiral biphenyl backbones **L135–L140**, comprising both phosphine and phosphite moieties, allowed the formation of 1,4-addition products from chalcone derivatives and acyclic aliphatic enones with ee up to 97%.⁹³ Highly remarkable is the finding that replacement of the chiral biphenyl moiety in **L138**, **L140** with a racemic unit as in **L141**, **L142** did not compromise the excellent enantioselectivity (up to 96% ee) in the addition of diethylzinc to chalcone (Fig. 30).⁹⁴

Thioether-phosphinites **L143–L145**, and diphosphinite ligands **L146**, **L147** based on a D-xylose scaffold were used in the conjugate addition of diethylzinc or triethylaluminium to 2-cyclohexen-1-one. After optimization, only moderate enantioselectivities were observed in both cases (up to 64% and 48% ee, respectively) (Fig. 31).⁹⁵

Bidentate sugar-phosphite-oxazoline **L148** and phosphite-phosphoramidite ligands **L149** have been screened in the conjugate addition of trimethyl and triethylaluminium to cyclic and acyclic enones. Ee's up to 80% were obtained using **L148** which contains encumbered biaryl phosphite moieties and a phenyl oxazoline group (Fig. 32).⁹⁶

Planar-chiral phosphoferrocene ligands **L150–L152** proved to be efficient in the enantioselective conjugate addition of diethylzinc to chalcone derivatives, with ee's up to 91% (Fig. 33).⁹⁷ The dominant stereocontrol element in these 1,4-addition reactions is the central chirality of the oxazolidine subunit of the ligand and not the planar chirality of the phosphoferrocene. Moreover, a study of the relationship between the ee of the product compared to the ee of the ligand showed a negative nonlinear effect, suggesting the presence of heterochiral bis- (or higher) ligated complexes.

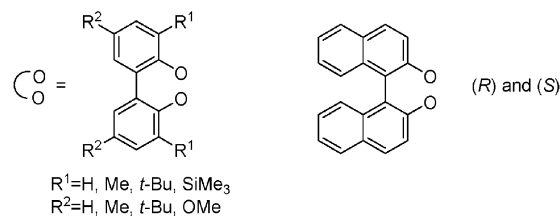


Fig. 32 Bidentate sugar-phosphite-oxazoline and phosphite-phosphoramidite ligands.

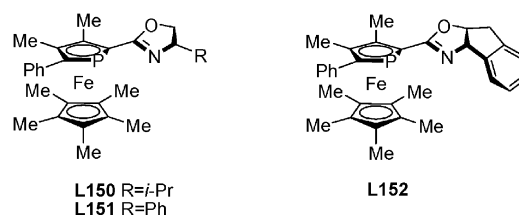


Fig. 33 Planar-chiral phosphoferrocene ligands.

3. Non-phosphorus ligands

Hoveyda and Hird investigated the asymmetric conjugate addition of dialkylzinc reagents to tetrasubstituted cyclic enones using peptide-based phosphine ligand but only racemic products were found. A new library of non-phosphorus containing peptide-based ligands **L153–L158** was designed (Fig. 34).⁹⁸ After screening and optimization, using a combination of 2 mol% of air-stable CuCN and 2 mol% of aniline-based ligand **L159**, the addition of dialkylzinc to tetrasubstituted enones was successfully executed. A stereogenic quaternary centre was created in good to excellent yields and enantioselectivities (up to 95% ee) (Scheme 30).

In 2001, Woodward and Fraser reported a highly active catalyst for the conjugate addition of diethylzinc to 2-cyclohexen-1-one based on an achiral Arduengo-type diamino-carbene as ligand.⁹⁹ In the same year, the first examples of asymmetric 1,4-addition of diethylzinc to cyclic and aliphatic

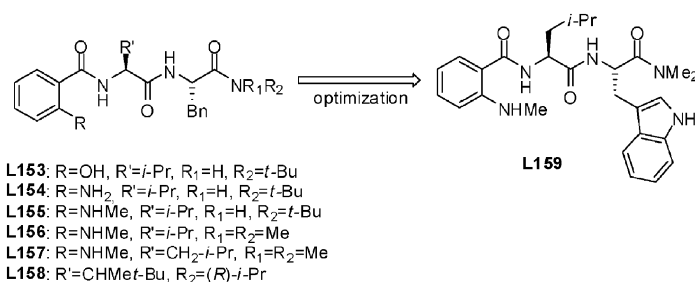
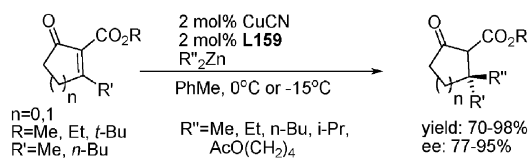


Fig. 34 Optimization of peptide-based ligand for 1,4-addition of dialkylzinc reagents to tetrasubstituted enones.



Scheme 30 1,4-Addition of dialkylzinc reagents to tetrasubstituted enones.

α,β -unsaturated enones with chiral diaminocarbenes were described. The reaction rate was high (98% yield in 15 min) but the enantiomeric excess was low (23% ee).¹⁰⁰ A library of chiral *N*-heterocyclic carbenes **L160–L168** was developed but even after optimization only modest ee's (up to 54%) were obtained in asymmetric conjugate addition (Fig. 35).¹⁰¹

Introducing a second coordination site at the diamino-carbene ligand, as provided by an alcohol moiety, gave bidentate alkoxy-*N*-heterocyclic carbene ligands **L169–L174**. These ligands showed higher enantioselectivities in the asymmetric conjugate addition of diethylzinc to cyclic enones (Fig. 36).¹⁰² Using only 2 mol% Cu(OTf)₂ and 3 mol% **L170**, good enantioselectivities were obtained at room temperature.¹⁰³ However, lower enantioselectivities were obtained with acyclic α,β -unsaturated ketones and nitroalkenes.¹⁰⁴

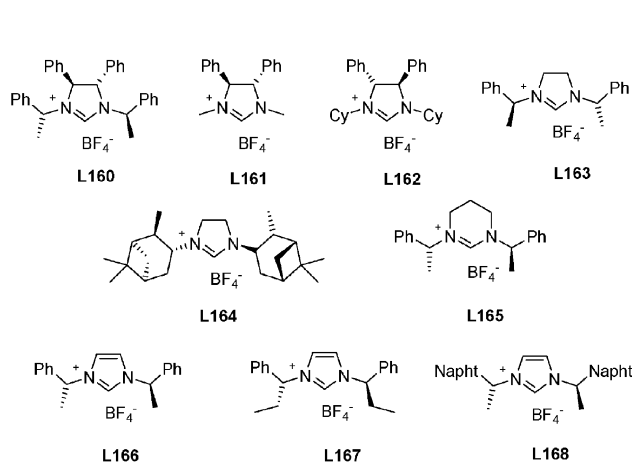


Fig. 35 Chiral diaminocarbene ligands.

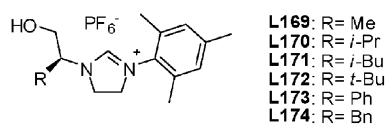


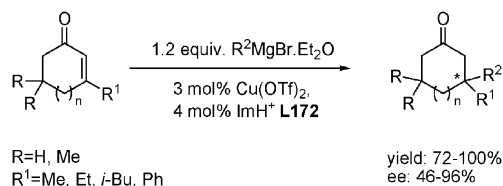
Fig. 36 Bidentate alkoxy-*N*-heterocyclic carbene ligands.

Conjugate addition of Grignard reagents to trisubstituted enones using phosphoramidite or ferrocene-based ligands gave only low enantioselectivities. A breakthrough was achieved by Alexakis *et al.* using a library of diaminocarbene ligands **L172** and Cu(OTf)₂ as copper source. The reaction proceeded fast and high enantioselectivities (46–96% ee) were obtained in 30 min in excellent yields (72–100%) in the 1,4-addition to β -substituted cyclic enones (Scheme 31).¹⁰⁵

The use of silver–carbene complex **L175–L179** in the asymmetric conjugate addition of diethylzinc to 2-cyclohexen-1-one increased the enantioselectivity with ee's up to 69%. Higher selectivities were obtained using cycloheptenone as substrate (93% ee) (Fig. 37).¹⁰¹

The combination of bidentate silver–carbene complex **L180** and Cu(OTf)₂·C₆H₆ was also used to promote copper-catalyzed conjugate addition of dialkyl- and diarylzinc reagents to β -substituted- α,β -unsaturated cyclic ketones (Fig. 38).¹⁰⁶

Using dialkylzincs, 1,4-addition products with quaternary centres were obtained in good yield and 54–95% ee (Scheme 32). Transformations with diarylzincs proceeded less readily than those involving dialkylzinc reagents but with



Scheme 31 1,4-Addition of Grignard reagents to β -substituted cyclic enones.

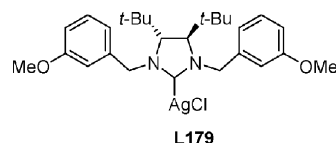
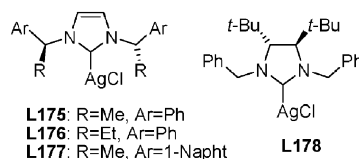


Fig. 37 Silver–carbene complexes.

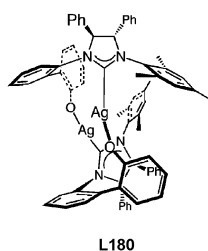
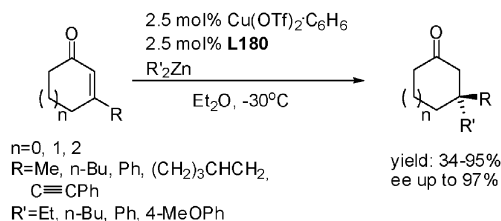


Fig. 38 Dimer of silver–carbene complexes.



Scheme 32 1,4-Addition of dialkyl- and diarylzincs to β -substituted cyclic enones.

higher enantioselectivity (ee up to 97%). Moreover, copper-catalyzed asymmetric conjugate addition of dialkylzincs generated the opposite absolute configuration, compared to reactions with diarylzincs.

A number of other ligand structures have shown promising enantioselectivities in the conjugate addition of dialkylzinc reagents. These include thieno[3',2':4,5]cyclopenta[1,2-*d*]-[1,3]oxazoline ligands **L181–L185** which in combination with $\text{Cu}(\text{OTf})_2$ have been used in the 1,4-addition of diethylzinc to chalcones, leading to the alkylated product in 40–61% yields with enantioselectivities ranging from 43 to 79% (Fig. 39).¹⁰⁷

1,4-Addition of diethylzinc to cyclic, acyclic enones and nitrostyrene derivatives using a combination of 2 mol% of $\text{Cu}(\text{OTf})_2$ or $\text{Cu}(\text{OAc})_2$ and a slight excess of thio-substituted binol-derived ligands **L186**, **L187** (Fig. 40) afforded β -alkylated adducts in good to excellent yields (74–96%) and enantioselectivities (70–96%).¹⁰⁸

Van Koten and co-workers investigated the behaviour of well-defined copper(i)-aminoarenethiolate complexes **L188–L192** in the asymmetric conjugate addition of diethylzinc and Grignard reagents to α,β -unsaturated cyclic and acyclic enones (Fig. 41).¹⁰⁹ Whereas addition of Grignard reagents afforded better enantioselectivity with acyclic enones (up to 76%), the best results were obtained in the addition of diethylzinc to cyclic α,β -unsaturated ketones (up to 83% ee). Moreover, a positive non-linear relation between the ee of the catalyst and the ee of the product was observed.

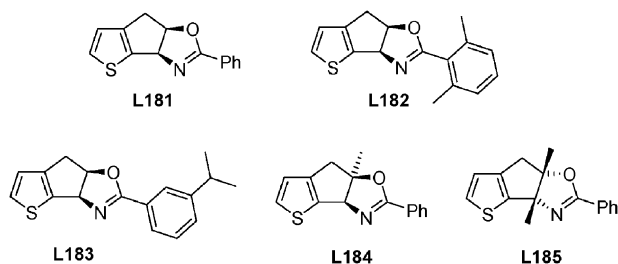


Fig. 39 Thieno[3',2':4,5]cyclopenta[1,2-*d*][1,3]oxazoline ligands.

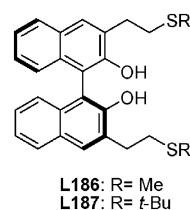


Fig. 40 3,3'-Thio-substituted binol-derived ligands.

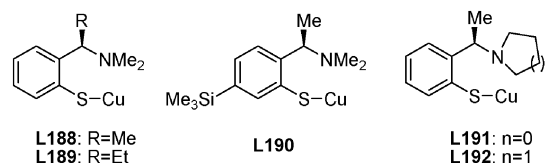


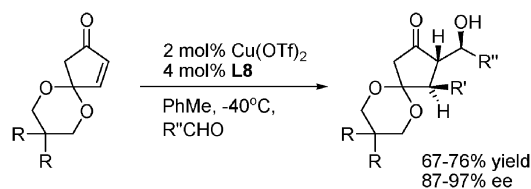
Fig. 41 Copper (i)-aminoarenethiolate complexes.

4. Trapping and tandem reactions

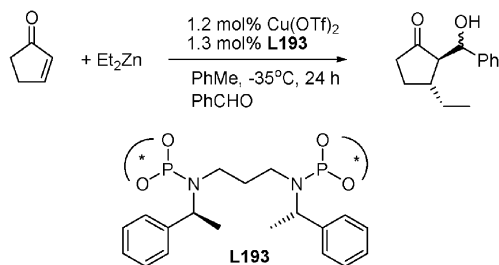
With the advances made in the asymmetric conjugate addition of dialkylzinc reagents to cyclic and acyclic enones, several approaches to accomplish tandem reactions using the enantioselective copper-catalyzed 1,4-addition followed by trapping of the intermediate enolate emerged.¹¹⁰ This resulted in the synthesis of highly functionalised molecules in a one pot operation. The products are frequently highly versatile building blocks for the synthesis of natural and/or pharmaceutical compounds.¹¹¹ In this field, pioneering works were done by Feringa and co-workers in 1997 when the first highly efficient catalytic asymmetric tandem 1,4-addition–aldol reactions were described.¹⁴ In 2001, enantioselective tandem 1,4-addition–aldol reactions were reported by the same group as the basis for a concise synthesis of prostaglandin-E1. The tandem 1,4-addition–aldol reaction of dialkylzinc reagents to cyclopentene-3,5-dione monoacetals in the presence of aldehydes using copper(ii) triflate in combination with monodentate phosphoramidite ligand **L8** proceeds with excellent enantioselectivity (Scheme 33).¹¹²

The use of bidentate phosphoramidite ligands, with either binol or taddol moieties **L193**, in the 1,4-addition of diethylzinc to 2-cyclopenten-1-one in the presence of 1.2 mol% of $\text{Cu}(\text{OTf})_2$ led to the formation of the corresponding β -hydroxyketone in 83% ee. Unfortunately, the influence of the ligand during the subsequent aldol reaction was minor, resulting in a mixture of *trans,erythro* and *trans,threo* products with ratios up to 35 : 65 (Scheme 34).¹¹³

Amino acid based chiral phosphine ligands **L194**, and **L195** were used by Hoveyda *et al.* to effect efficient enantioselective tandem 1,4-addition–aldol reaction of dialkylzinc reagents to small and medium ring unsaturated lactones and pyranone



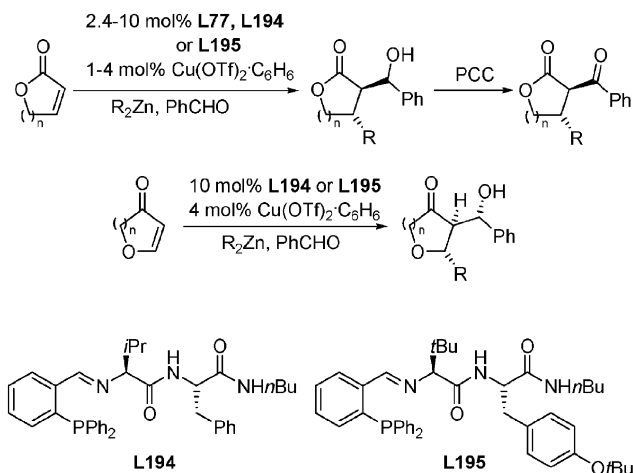
Scheme 33 Tandem 1,4-addition–aldol reaction of dialkylzinc reagents to cyclopentene-3,5-dione monoacetals.



Scheme 34 Tandem 1,4-addition-aldol reaction of diethylzinc to cyclopenten-1-one.

derivatives. The resulting aldol products were oxidized to afford the corresponding diketones in good yield and excellent ee and de (Scheme 35).¹¹⁴

Silyl enol ethers can be synthesized from enones *via* the tandem asymmetric conjugate addition-silylation reaction.¹¹⁵ Zinc enolates resulting from the copper catalyzed addition of dialkylzinc to 2-cyclohexen-1-one in the presence of

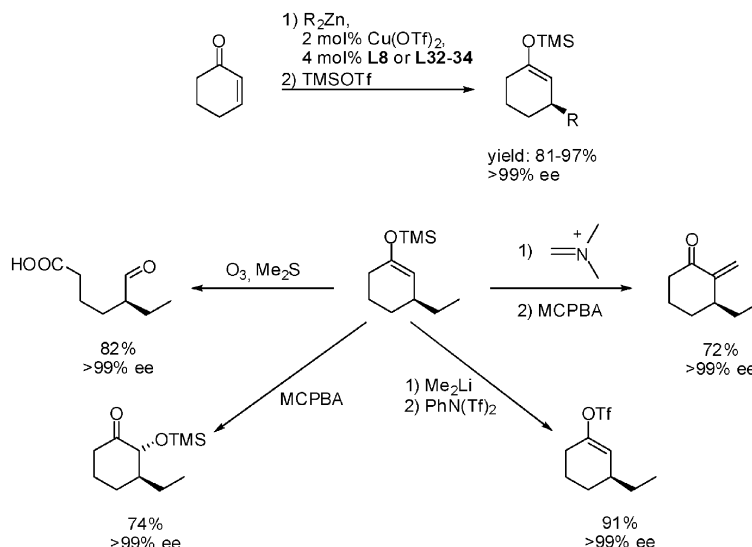


Scheme 35 Tandem 1,4-addition-aldol reaction of diethylzinc to unsaturated lactones and pyranone derivatives.

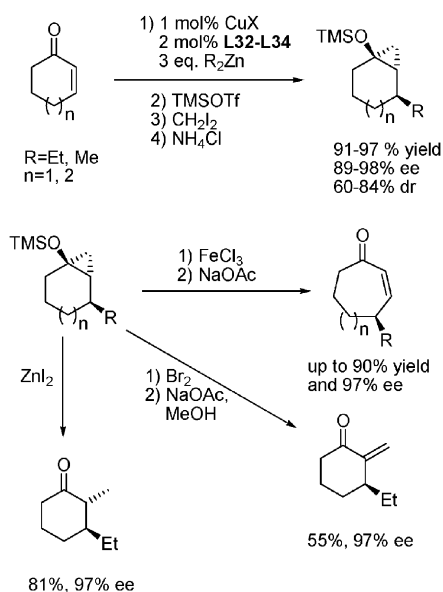
phosphoramidite ligand **L8** and **L32–34** were trapped in apolar solvents using trimethylsilyl triflate to afford silyl enol ethers in yields up to 97% (Scheme 36). Zinc enolates derived from acyclic enones were found to be configurationally stable, as evident from the stereochemistry of the resulting silyl enol ethers and the fact that the enantiomeric excess of silyl enol ethers was not dependent on the preferred (*s-trans* or *s-cis*) configuration of the acyclic substrate. As many transformations can be readily performed using these silyl enol ethers, a broad range of interesting optically active synthons is accessible in one additional step in good yield.

An efficient asymmetric one-pot synthesis of cyclic and linear silylated cyclopropanols *via* a tandem 1,4-addition-cyclopropanation was developed by Alexakis and March using 1 mol% of copper(I) or copper(II) sources and 2 mol% of chiral monodentate phosphoramidite ligands **L32–L34** based on a diphenyl backbone (Scheme 37).¹¹⁶ The use of 3 equiv. of diorganozinc reagent was required to trap the zinc enolate and to generate *in situ* from diiodomethane cyclopropanation reagent MeZnCH₂I. After reaction with trimethylsilyltriflate and diiodomethane, silylated cyclopropanols were obtained with excellent yields and enantioselectivities and good diastereomeric ratios.

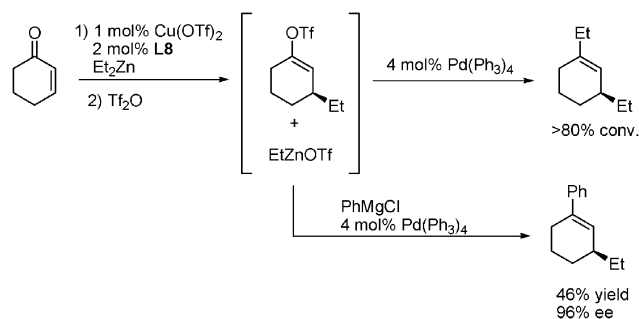
Enantiomerically enriched hydrocarbons can be synthesized from 2-cyclohexen-1-one involving a tandem enantioselective 1,4-addition-trapping reaction as key step (Scheme 38).¹¹⁷ Using a low loading of copper(II) triflate and phosphoramidite ligand **L8** (1 mol% and 2 mol%, respectively), the corresponding vinyl triflate was obtained in 97% ee. The palladium-catalyzed coupling between the vinyl triflate and EtZnOTf, both formed *in situ* by the addition of triflic anhydride to the zinc enolate led to the chiral olefin. This illustrated that the appropriate combination of the two metal-catalyzed transformations can lead to the transfer of both alkyl groups from the diorganozinc reagent to the enone. Using phenylzinc chloride as reagent for the cross-coupling reaction, a mixture of products is obtained resulting from the competition with ethylzinc triflate. To overcome the problem, the more reactive



Scheme 36 Versatility of silyl enol ethers obtained *via* tandem conjugate addition-silylation.



Scheme 37 Synthesis of silylated cyclopropanols and versatility in synthesis.

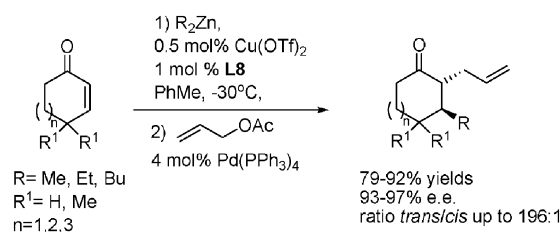


Scheme 38 Synthesis of vinyl triflates *via* tandem 1,4-addition-trapping reactions.

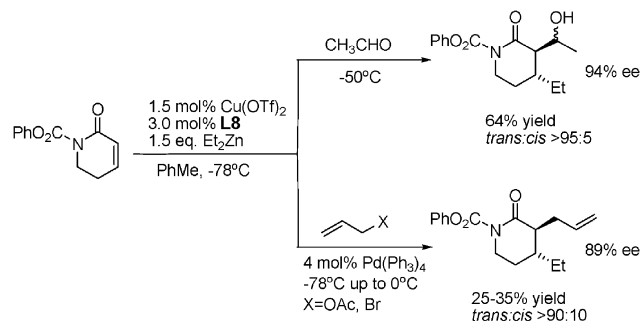
Grignard reagent was used in the second step allowing the isolation of the chiral olefin with high enantioselectivity.

This procedure was highly versatile in the synthesis of bicyclic compounds and the total synthesis of the potent neurotoxin (–)-pumiliotoxin C was described using a very low loading of copper triflate and phosphoramidite ligand **L8** (Fig. 1). A tandem asymmetric 1,4-addition-allylic substitution as key step was developed by Feringa and co-workers (Scheme 39).¹¹⁸ The synthesis started with the copper-phosphoramidite catalyzed addition of dialkylzinc to 2-cyclohexen-1-one with excellent enantioselectivities (up to 97%). The resulting zinc enolate reacted then with allyl acetate in the presence of a catalytic amount of Pd(PPh₃)₄, affording the disubstituted cyclohexanones in good to excellent yields and very high ratios of *trans/cis* isomers (up to 196/1).

The same strategy was used in the trapping of the intermediate zinc enolate derived from the conjugate addition of diethylzinc to an unsaturated lactam using monodentate phosphoramidite ligand **L8**. With acetaldehyde at –50 °C *trans*-3,4-disubstituted 2-piperidinone was obtained as an inseparable mixture of aldol isomers with 94% ee (Scheme 40).³⁰ The same zinc-enolate intermediate can be trapped in a



Scheme 39 Tandem 1,4-addition-allylation reaction.



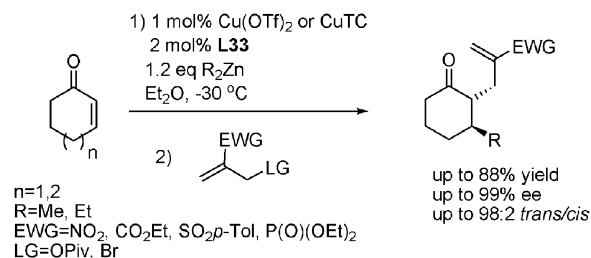
Scheme 40 Tandem 1,4-addition-aldol and 1,4-addition-allylation reactions.

one-pot procedure by allyl bromide or allyl acetate and 4 mol% of Pd(PPh₃)₄ to deliver an allyl-substituted piperidinone with 89% ee, albeit in only 25–35% isolated yield.

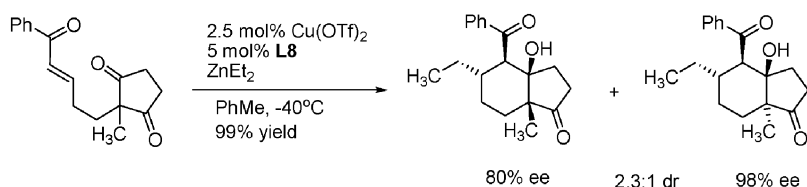
A related one-pot procedure for the copper-catalyzed 1,4-addition-allylic alkylation was reported by Alexakis.¹¹⁹ Using 1 mol% of copper source and 2 mol% of monodentate phosphoramidite ligand **L33** in the conjugate addition of dialkylzincs to cyclohexenone, the resulting zinc enolate was trapped with activated allylic substrates without additional catalyst to afford the desired product in good yields and excellent enantioselectivity and *trans/cis* ratio (Scheme 41).

Krische and co-workers reported the use of ketones, esters and nitriles as trapping agents in the copper-catalyzed conjugate addition-intramolecular electrophilic trapping reaction using achiral phosphites.¹²⁰ One example was reported using 5 mol% of the chiral phosphoramidite ligand **L8** and 2.5 mol% of copper(II) triflate in the addition of diethylzinc to an enone-dione substrate. The tandem reaction quantitatively afforded highly functionalized bicyclic compounds possessing four contiguous stereogenic centres with a *cis* : *trans* ratio of 2.3 : 1 in 80% and 98% ee, respectively (Scheme 42).

Enantioselective conjugate addition of dialkylzincs in the presence of Cu(OTf)₂ and chiral monodentate phosphoramidite ligands to bis- α,β -unsaturated enones followed by



Scheme 41 Tandem 1,4-addition-allylic alkylation reactions.



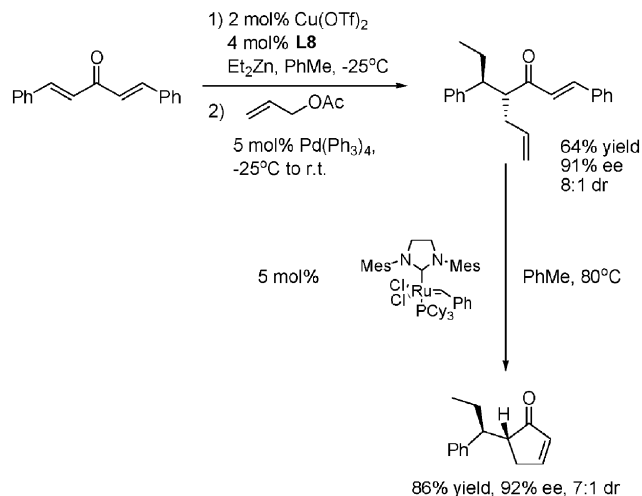
Scheme 42 Tandem 1,4-addition–intramolecular electrophilic trapping reaction.

the intramolecular trapping of the zinc enolate was reported by Alexakis (Scheme 43).¹²¹ With 2 mol% of copper(II) triflate and 4 mol% of **L35**, cyclic and heterocyclic compounds with multi-chiral centres were formed as a mixture of two diastereoisomers with excellent enantioselectivities (up to 94% ee). The stereochemistry was found to be highly in favor of *trans,trans* products (up to 99 : 1).

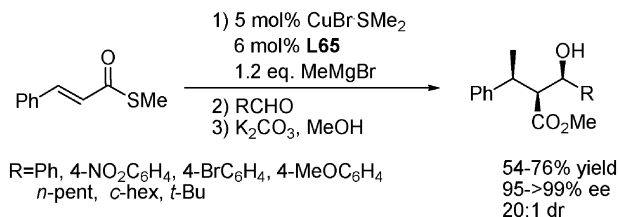
α -Bromo- β -alkyl ketones can be synthesized in a one-pot reaction from α,β -unsaturated ketones, using $\text{Cu}(\text{OTf})_2$ as the copper precursor, monodentate phosphoramidite ligands **L8**, **L34**, **L35**, **L39**, and bromine as the trapping electrophile (Scheme 44).¹²² Ee's up to 98% were obtained using cyclic ketones but lower enantioselectivities were obtained with linear substrates (up to 90%). However, in both cases, diastereoisomeric ratios were moderate (up to 74 : 26). The synthetic potential of this methodology was illustrated by the radical mediated cyclisation of the α -brominated ketone adducts.

The zinc enolate resulting from the conjugate addition of diethylzinc to dienones in the presence of $\text{Cu}(\text{OTf})_2$ and chiral phosphoramidite **L8** was trapped with allyl acetate in a diastereoselective palladium-catalyzed allylation in high enantioselectivity and diastereoselectivity (Scheme 45).²⁵ The presence of the two suitably located olefins allowed the cyclisation reaction to be performed. After ring-closing metathesis, using 5 mol% of the second generation Grubbs' catalyst, chiral substituted cyclopentenone was obtained with a *cis* : *trans* ratio of 7 : 1 in high yield and 92% ee.

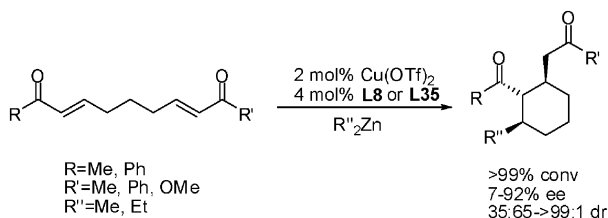
The first use of Grignard reagents in the tandem enantioselective copper catalyzed 1,4-addition–aldol reaction was reported in 2006 by Feringa and co-workers.¹²³ Highly yields



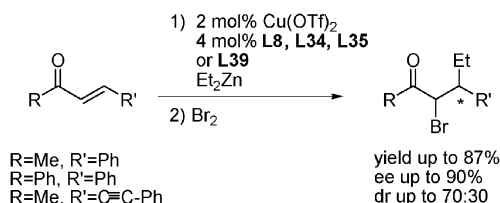
Scheme 45 Synthesis of chiral substituted cyclopentenone.



Scheme 46 Tandem catalyzed enantioselective 1,4-addition–aldol reaction.



Scheme 43 1,4-Addition followed by intramolecular trapping reaction.



Scheme 44 Trapping reaction in the synthesis of α -bromo- β -alkyl ketones.

and enantioselectivities were obtained in addition of Grignard reagents to acyclic α,β -unsaturated thioesters where the resulting magnesium enolates were trapped with aromatic or aliphatic aldehydes (Scheme 46). The process required a low loading of bidentate Josiphos ligand **L65** (Fig. 8) and $\text{CuBr}\cdot\text{SMe}_2$ as copper source and provided a wide scope of tandem products, bearing three contiguous stereocentres. Excellent control of relative and absolute stereochemistry was achieved. After methanolysis, products were isolated as their methyl esters in good yield and high enantio and diastereoselectivities (up to 99% ee and 20 : 1 dr) (also see Scheme 63).

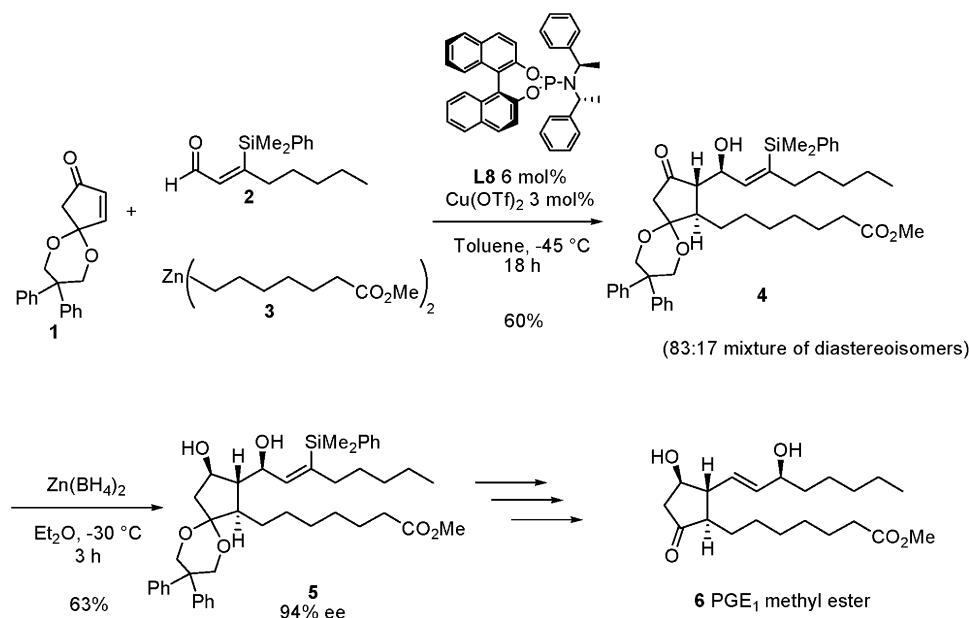
5. Synthetic applications

The synthetic utility of the copper-catalyzed 1,4-addition of organometallic reagents has been demonstrated by its application as a key step in numerous syntheses of natural products and biologically active compounds.^{124,125} A notable example is the use of a tandem 1,4-addition–enolate-trapping reaction in the synthesis of prostaglandins PGE₁ methyl ester **6** reported

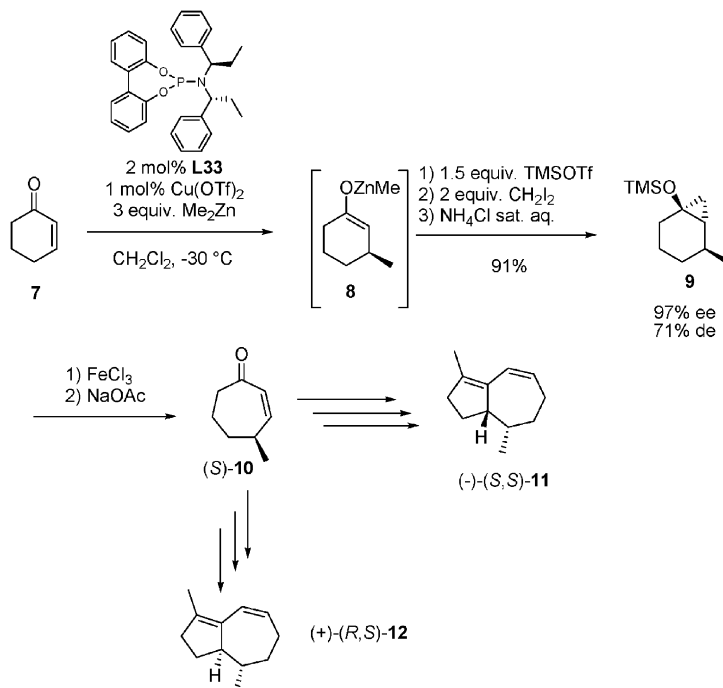
by Minnaard, Feringa and co-workers (Scheme 47).¹²⁶ The synthetic approach followed is reminiscent of the three-component coupling reaction introduced by Noyori.¹²⁷ The enantioselective 1,4-addition of ester-functionalized zinc reagent **3** to cyclopentene-3,5-dione monoacetal **1** in the presence of $\text{Cu}(\text{OTf})_2$ and the chiral phosphoramidite **L8** was followed by the trapping of the zinc enolate with aldehyde **2**. This tandem procedure afforded compound **4** in 60% yield as a mixture of diastereoisomers (*trans,threo* : *trans,erythro* ratio 83 : 17). After reduction of the ketone moiety to the corresponding alcohol, the major diastereoisomer **5**, featuring

all structural and stereochemical elements of PGE_1 methyl ester, could be isolated in 63% yield and 94% ee.

A tandem enantioselective conjugate addition–cyclopropanation sequence has been used by Alexakis and March as a key step in the formal synthesis of the sesquiterpenes (–)-(*S,S*)-clavukerin A **11** and (+)-(*R,S*)-isoclavukerin **12**.¹¹⁶ Starting from cyclohexenone **7**, 1,4-addition of Me_2Zn was performed using 1 mol% of $\text{Cu}(\text{OTf})_2$ and 2 mol% of **L33** (Scheme 48). The zinc enolate **8** was silylated with TMSOTf and the resulting silylenolate was cyclopropanated in the presence of diiodomethane. Compound **9** was obtained in high yield



Scheme 47 Synthesis of PGE_1 .

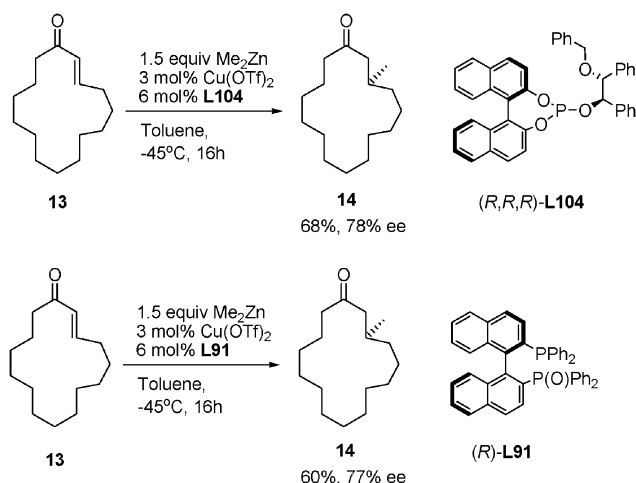


Scheme 48 Synthesis of (–)-(*S,S*)-clavukerin A and (+)-(*R,S*)-isoclavukerin.

(91%) and enantioselectivity (97%). The π -face selectivity of the cyclopropanation was only modest (71% de), however the disappearance of these stereocentres in the sequential transformation to compound **10** renders the low de value unimportant.

In 2003 a straightforward asymmetric synthesis of (*R*)-(-)-muscone **14**, the key flavour component of musk, was achieved *via* conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one **13** albeit with modest enantioselectivity.⁷⁷ The use of phosphite **L104** as chiral ligand in combination with Cu(OTf)₂ afforded the desired product in 68% yield and 78% ee after 2 h (Scheme 49). The conjugate addition of Me₃Al to **13** in the presence of Cu(CH₃CN)₄PF₆ and ligand **L91** affords (*R*)-(-)-muscone **14** in 60% isolated yield and with 77% ee.⁶⁹

Nitroolefins represent an important class of acceptors in 1,4-addition reactions due to the versatility of the nitro group in organic synthesis. Enantioselective 1,4-addition to nitroalkenes provides an attractive route to β^2 -amino acids and derivatives, which are important building blocks in the synthesis of natural products, β -peptides and pharmaceuticals.³⁴ The copper-catalyzed addition of organozinc reagents to acetal substituted nitroalkenes was developed in our group.³⁵

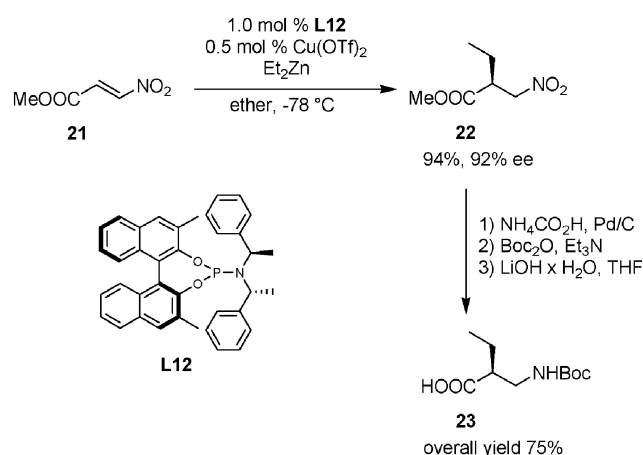


Scheme 49 Synthesis of (*R*)-(-)-muscone.

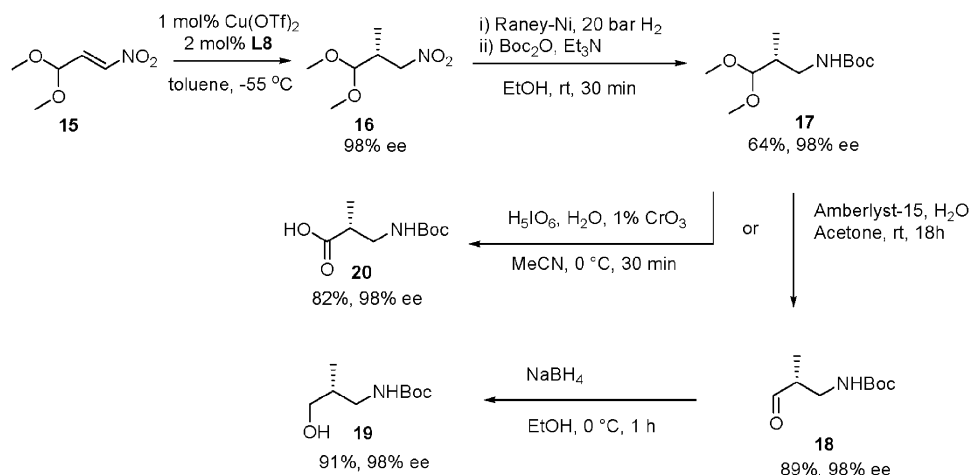
Using 1 mol% of Cu(OTf)₂ and 2 mol% of the chiral phosphoramidite **L8**, excellent results were obtained both in terms of yield and enantioselectivity in the conjugate addition of several organozinc reagents to substrate **15**. In particular, the conjugate addition products like **16** can be converted readily to the protected β -amino aldehydes, alcohols and acids (Scheme 50). For example, reduction of **16**, followed by Boc-protection and cleavage of the acetal provides the β -amino aldehyde **18**, a building block in the total synthesis of cyclamenol A.¹²⁸ Subsequent reduction of **18** gives the β -amino alcohol **19**, a starting material in the synthesis of β -methyl carbapenem antibiotics.¹²⁹ Compound **17** can also be oxidized to the *N*-Boc-protected β -amino acid **20**, used in the total synthesis of cryptophycins.¹³⁰

Sewald and Rinkus described the 1,4-addition of Et₂Zn to the activated nitroolefin methyl 3-nitropropenoate.³⁶ Ligand **L12** turns out to give the highest enantioselectivity, reaching 92% ee in the presence of only 0.5 mol% of the catalyst (Scheme 51). The β -nitroester **22** can easily be reduced, Boc-protected and subsequently saponified to give the β^2 -amino acid **23**.

Nitroolefins have proven to be useful also as starting materials in the synthesis of molecules belonging to the profen



Scheme 51 Synthesis of chiral amino acids from nitroalkenes.



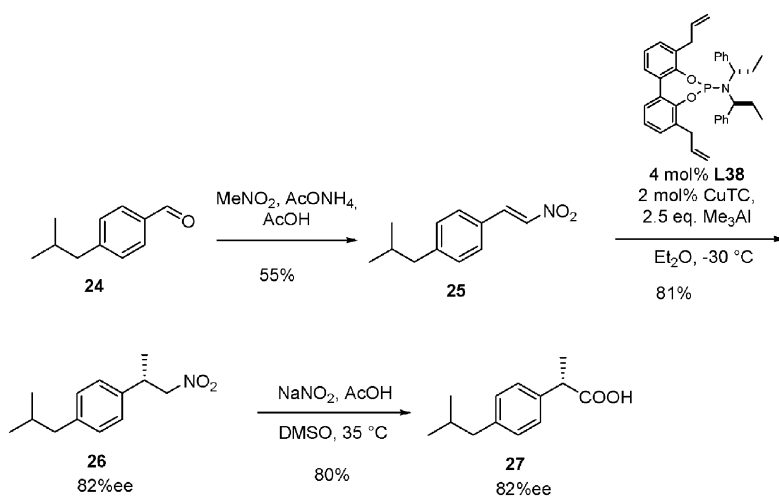
Scheme 50 Synthesis of protected β -amino aldehydes, alcohols and acids from nitroalkenes.

family, also. In particular, the asymmetric synthesis of (+)-ibuprofen, based on ACA has been described by Polet and Alexakis.⁴³ The introduction of the methyl substituent was achieved using Me_3Al instead of the less reactive Me_2Zn (Scheme 52). The α,β -unsaturated substrate is obtained *via* Henry condensation from compound **24**; conjugate addition in the presence of 2 mol% of copper thiophene carboxylate (CuTC) and 4 mol% of **L38** on nitroalkene **25** affords the β -methylated product **26** in good yield and 82% ee. Further functional group modification, according to literature procedures, provided (+)-ibuprofen **27**.

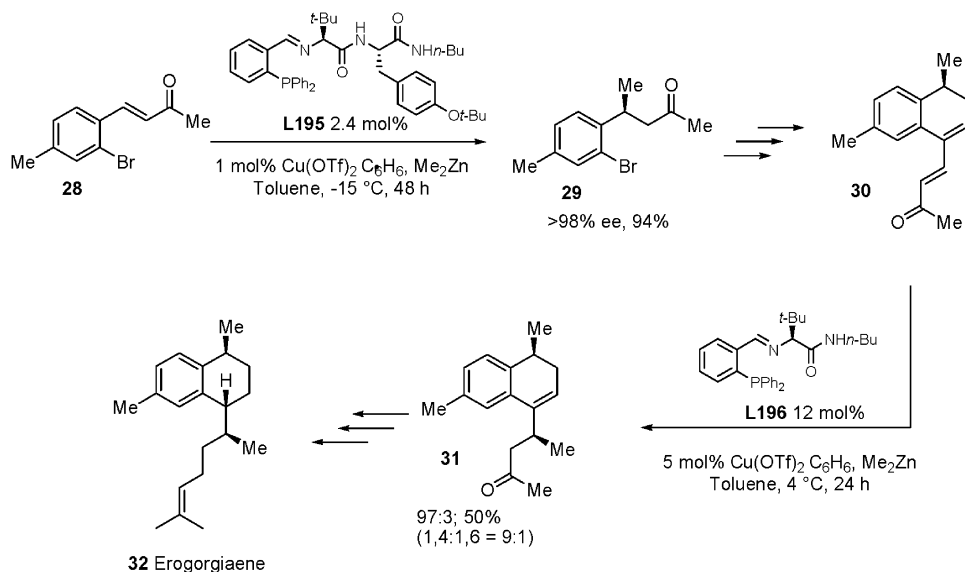
In 2004 Hoveyda *et al.* applied the asymmetric Cu-catalyzed conjugate addition of Me_2Zn to acyclic enones in the total synthesis of the antimycobacterial agent erogorgiaene **32** (Scheme 53).¹³¹ First, the α,β -unsaturated enone **28** underwent addition of Me_2Zn , on a multigram scale, in the presence of 1.0 mol% of $[(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6]$ and 2.4 mol% of chiral phosphine **L195**, to deliver β -methyl ketone **29** in 94% isolated

yield and more than 98% ee. This result is, at first glance, in contrast to the low reactivity shown in general by β -aryl-substituted acyclic enones in this type of reaction.⁵⁵ However detailed studies proved that the presence of a substituent at the *ortho* position of the phenyl ring, regardless of its electronic properties, was beneficial to the rate of the reaction. A second diastereoselective copper-catalyzed conjugate addition was performed on enone **30**; in this case the best results both in terms of diastereo- and regioselectivity were obtained using the chiral phosphine **L196** and increasing the catalyst loading to 5 mol%. A three-step conversion to **32** included a diastereoselective reduction which allowed for the introduction of the third stereocentre.

In the same year, Feringa, Minnaard and co-workers reported the asymmetric synthesis of (–)-pumiliotoxin C **36** based on two tandem catalytic reactions.¹¹⁸ A first tandem asymmetric conjugate addition–allylic substitution reaction, carried out on 2-cyclohexenone, allowed for the introduction



Scheme 52 Synthesis of (+)-ibuprofen.

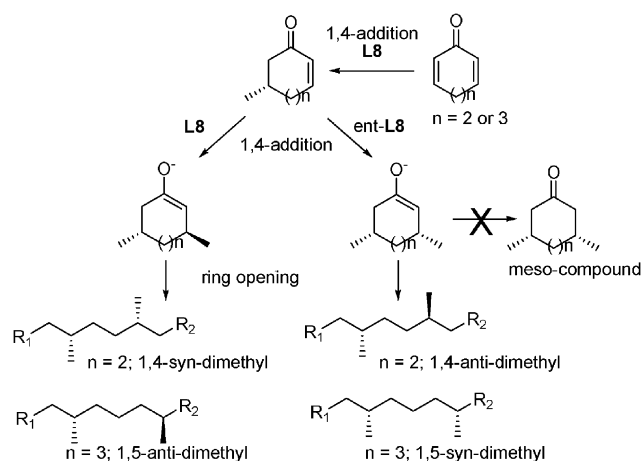


Scheme 53 Synthesis of erogorgiaene.

of two stereocentres providing **33** as a mixture of *trans*–*cis* isomers (ratio 8 : 1) in 84% yield and 96% ee (Scheme 54). Conversion of the carbonyl group into a *N*-tosylamine gave compound **34** which can undergo a tandem Heck–allylic substitution reaction¹³² to create the perhydroquinoline skeleton with both the natural and unnatural configuration at the C2 stereocentre (**35**). Two additional steps afforded the desired compound **36**.

Recently, Feringa, Minnaard and co-workers described the first catalytic procedure capable of preparing all 4 diastereoisomers of a versatile saturated isoprenoid building block.¹³³ This method is based on the iterative enantioselective conjugate addition of Me_2Zn to cyclic dienones which, after oxidative ring opening, allows to obtain enantiopure *syn*- and *anti*-dimethyl arrays in 1,4- or 1,5-relationship, according to the ring size of the starting cyclic enone (Scheme 55). The conjugate addition of Me_2Zn to the dienone in the presence of ligand **L8** allows the introduction of a methyl substituent with complete enantiocontrol. In the sequential conjugate addition, the use of the same chiral ligand **L8** or its enantiomer *ent*-**L8** results in a *trans* or a *cis* relationship of the two methyl substituents, respectively. In the case of the *cis*-adduct, quenching of the zinc enolate with a proton source generates a *meso* compound that, after ring opening, provided a racemic product. In order to avoid this loss of chiral information the enolate can be trapped *in situ* as a silyl enol ether before subsequent ring cleavage.

Scheme 56 gives an illustrative example of this method. Cycloocta-2,7-dienone **37** was subjected to conjugate addition of Me_2Zn to give compound **38** with complete enantiocontrol. A catalyst loading of 5 mol%, slow addition of the substrate as well as an excess of organozinc reagent (5.0 equiv.) are necessary to minimize the formation of side product **39**, due to Michael addition of the zinc enolate to the starting material (Scheme 56). Compound **38** can be subjected to a second conjugate addition of Me_2Zn . In this case the side reaction is not observed, allowing for a lower amount of catalyst (2.5 mol%) and Me_2Zn (1.5 equiv.) to be used. In the case of the *trans* adduct, the silyl enol ether **40a** can be obtained by trapping the zinc enolate with TMSOTf in the presence of TMEDA and Et_3N . In the case of the *cis* adduct, partial racemisation was observed using this trapping procedure.

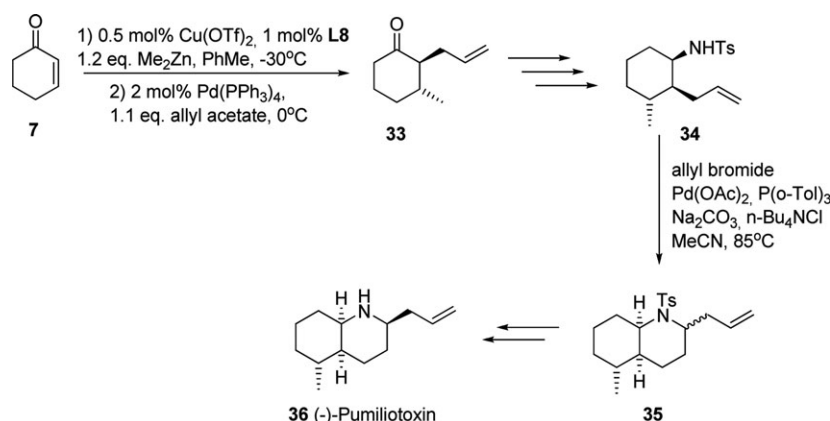


Scheme 55 Synthesis of chiral building blocks with 1,4- and 1,5-dimethyl arrays.

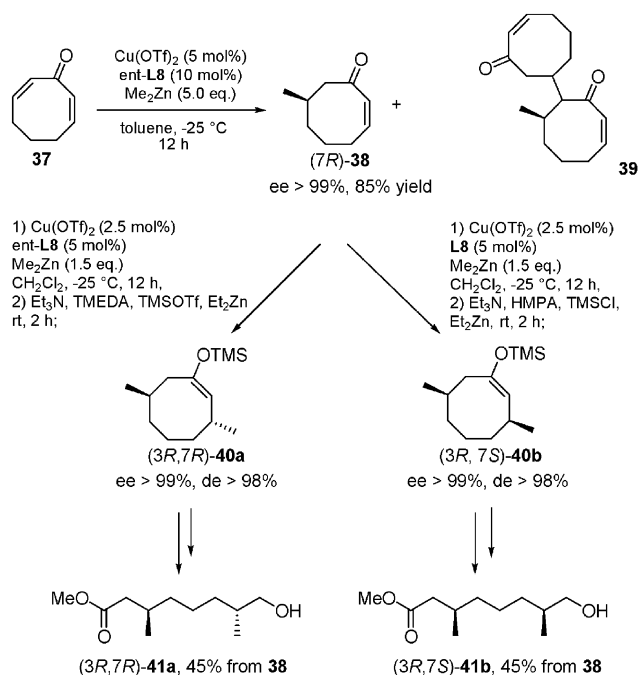
The use of TMSCl in the presence of HMPA and Et_3N , instead of TMSOTf, afforded compound **40b** enantiomerically pure and with high de (>98%). Ring opening *via* ozonolysis followed by reduction of the aldehyde to an alcohol and esterification of the free carboxylic acid gives the isoprenoid building block **41**.

A demonstration of the synthetic versatility of this catalytic protocol is seen in the total synthesis of two pheromones **46** and **47** produced by the female of the apple leafminer featuring an *anti*-1,5-array of methyl groups. Starting from compound **41a**, reduction of the ester moiety followed by chain elongations on both sides of the isoprenoid building block gives **46** and **47** in five steps (Scheme 57).

The synthetic versatility of isoprenoid building block **41** was demonstrated further in the total synthesis of β -mannosyl phosphomycoketide **56**, a potent mycobacterial antigen for T cells, isolated from *Mycobacterium tuberculosis*.¹³⁴ This natural product has a challenging array of 5 methyl groups in a 1,5-all-*syn* relationship. The synthetic scheme (Scheme 58) indicates that it is possible to build an acyclic structure with an array of four methyl groups **52**, *via* connection of the chiral building blocks **50** and **51**, which can be constructed starting from the same isoprenoid building block *ent*-**41b**. The



Scheme 54 Synthesis of (–)-pumiliotoxin C.



Scheme 56 Synthesis of *syn*- and *anti*-1,5-dimethyl arrays.

Julia–Kocienski coupling of **52** and fragment **53** allows introduction of the fifth methyl group with a *syn*-relationship. Interestingly, fragment **53** can be obtained through an enantioselective Cu-catalyzed 1,4-addition of MeMgBr to the linear α,β -unsaturated thioester **54** with 93% ee.¹³⁵

The construction of deoxypropionates and acyclic synthons in general with 1,3-arrays of methyl substitution, with *syn*- or *anti* stereochemistry, poses another major challenge to catalytic conjugate addition.¹³⁶ An iterative protocol for *syn*- and *anti*-deoxypropionates based on the Cu-catalyzed addition of Grignard reagents to α,β -unsaturated thioesters in the presence of Josiphos type ligands has been developed recently by Minnaard, Feringa and co-workers.¹³⁵ As depicted in Scheme 59, the conjugate addition of MeMgBr to thioester **57**, in the presence of 1 mol% of catalyst derived from $\text{CuBr}\cdot\text{SMe}_2$ and Josiphos **L65**, provides the β -methyl substituted compound **58** in excellent yield (93%) and enantioselectivity (95% ee). Fukuyama reduction¹³⁷ of the thioester moiety to the corresponding aldehyde followed by a Wittig

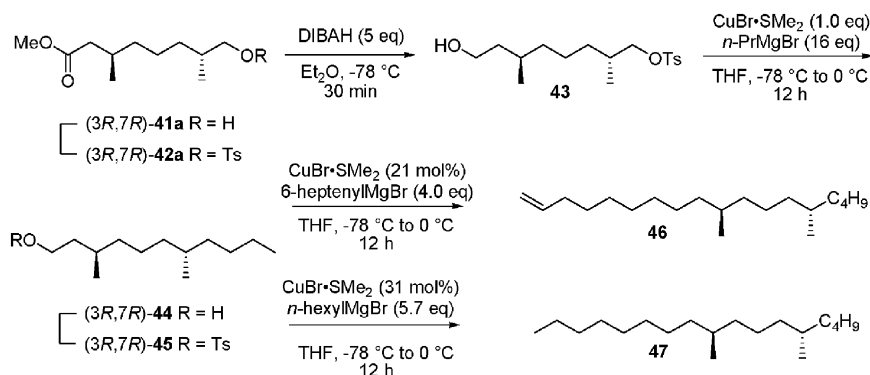
reaction affords the new Michael acceptor **60** again featuring an α,β -unsaturated thioester.

A second catalyzed conjugate addition reaction using **L65** or its enantiomer ent-L65 afforded with excellent yield (90%) and selectivity (dr 96 : 4) the *syn*- and *anti*-1,3-dimethyl derivatives **61** and **62**, respectively. The synthetic utility of this iterative process has been demonstrated in the asymmetric total synthesis of (–)-lardolure **68**, a pheromone of the acarid mite *Lardoglyphus konoi* (Scheme 60).¹³⁵ The iterative sequence allows for the formation of compound **65**, in which three methyl groups have been introduced by catalyzed conjugate addition with *syn* stereochemistry and de >95%. Modification of the thioester functional group afforded the target compound **68** in four additional steps.

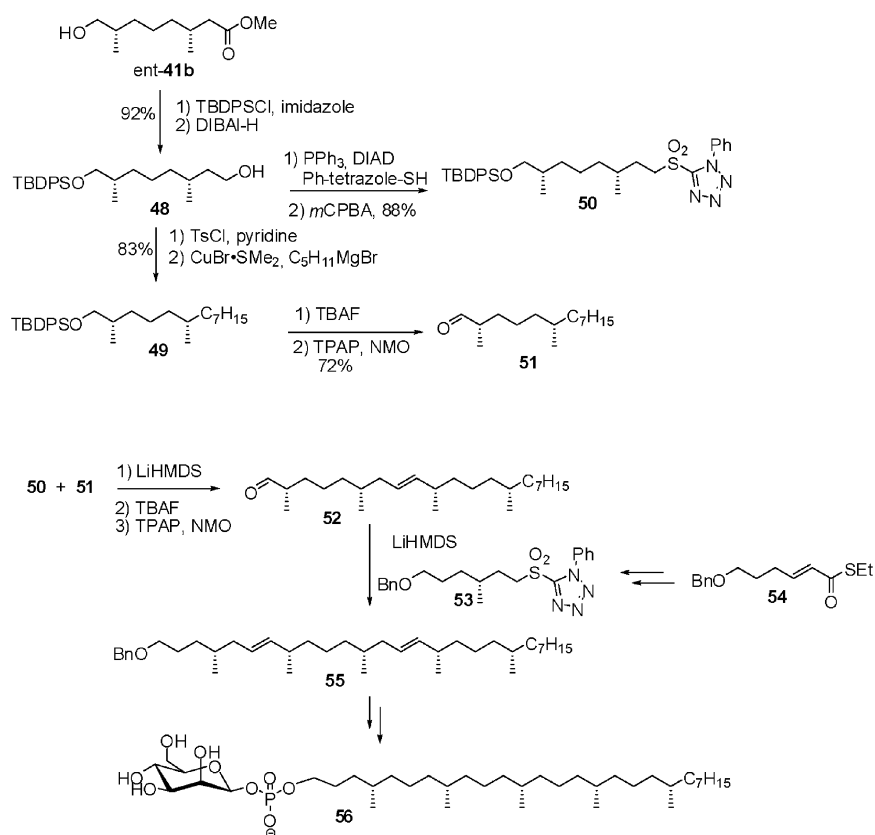
The same iterative sequence for the formation of 1,3-methyl arrays has been applied in the asymmetric syntheses of myco-cerosic acid **72**, one of the many methyl-branched fatty acids from *Mycobacterium tuberculosis* and the related tetramethyl-substituted fatty acid **73**, found in the preen-gland wax of the greylag goose *Anser anser* (Scheme 61).⁴⁹ The reaction protocol was applied four times in an iterative manner to arrive at the tetramethyl substituted compound **70** in ten steps with excellent selectivity and an overall yield of 21% from **69**. Two-fold reduction of thioester **70** with DIBAL-H and reaction of the obtained alcohol with TsCl gave silyl ether **71**, a common intermediate in the synthesis of the fatty acids **72** and **73**.

Continued iteration, starting with unsaturated thioester **69**, allows for the introduction of seven methyl groups to yield compound **74**, which was used for the synthesis of phthioceranic acid **76**. This is a fatty acid from the virulence factor Sulfolipid-I, found in *Mycobacterium tuberculosis* (Scheme 62).⁴⁹ The same route to the tosylated derivative **75** was followed. Elongation of the aliphatic chain and introduction of the carboxylic acid moiety afforded the all-*syn* compound **76** in 4% yield over 24 steps.

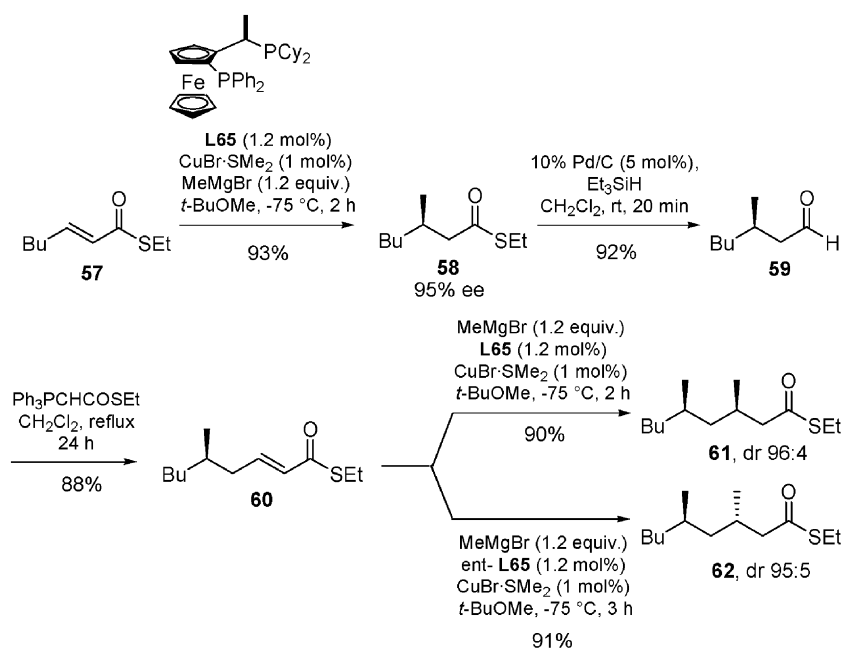
The synthetic versatility of the thioester moiety was also demonstrated in the synthesis of (–)-phaseolinic acid **81** from the paraconic acid family, representing an important class of biologically active compounds. The 1,4-addition–aldol method affords the target compound **81** in only four steps (Scheme 63).¹²³ The 1,4-addition of MeMgBr to unsaturated thioester **77** proceeds with high enantioselectivity (95%) all *syn* and after trapping of the magnesium enolate with hexanal, the tandem product **78** was obtained with remarkable



Scheme 57 Synthesis of female apple leafminer pheromones.



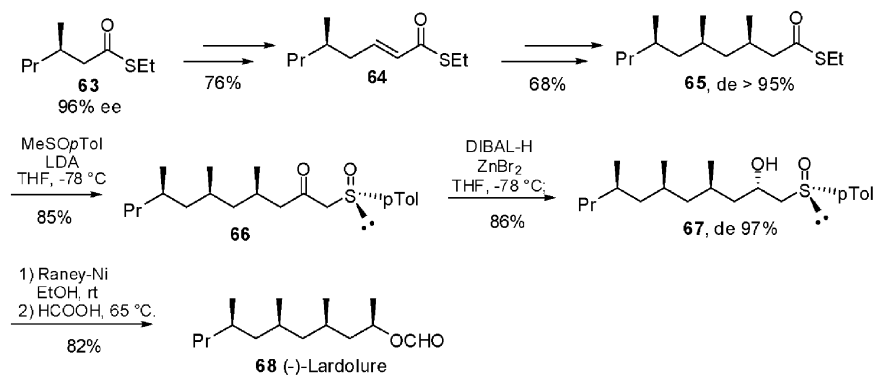
Scheme 58 Synthesis of β -mannosyl phosphomycoketide.



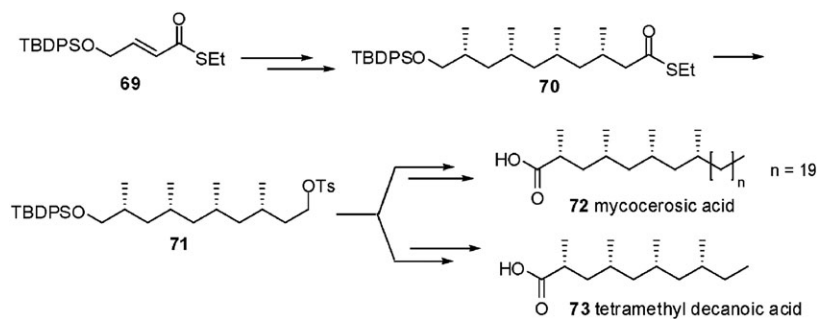
Scheme 59 Synthesis of *syn*- and *anti*-deoxypropionates.

stereocontrol as a single diastereoisomer in 72% yield. Protection of the free alcohol and catalytic oxidation of the aromatic ring afford compound **80**, which was transformed in (–)-phaseolinic acid by treatment with HBr (48%).

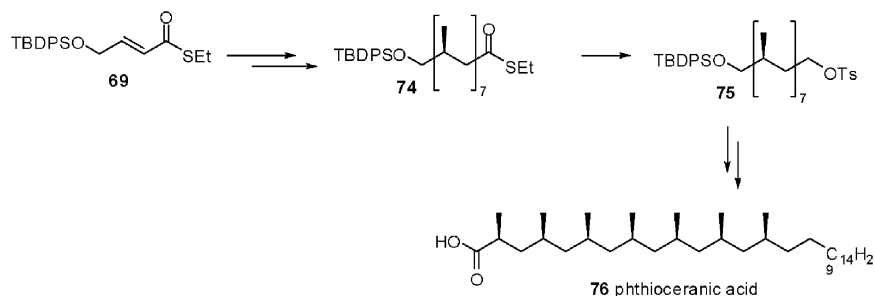
The high *syn*-selectivity of the aldol product can be rationalized in terms of a chair-like Zimmerman–Traxler transition state in which the large phenyl substituent on the aldehyde assumes a pseudoequatorial position to minimize



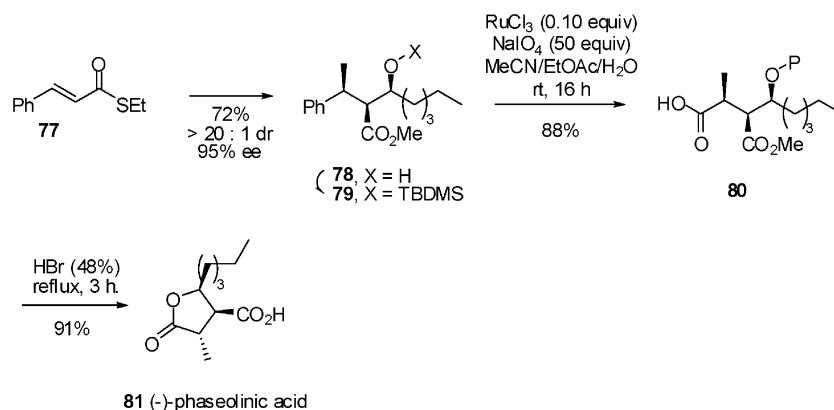
Scheme 60 Synthesis of (-)-lardolure.



Scheme 61 Synthesis of mycocerosic acid and tetramethyl-decanoic acid.



Scheme 62 Synthesis of phthioceranic acid.



Scheme 63 Synthesis of (-)-phaseolinic acid.

unfavourable diaxial interactions (Fig. 42a). In the resulting transition state, minimization of the *syn*-pentane interaction

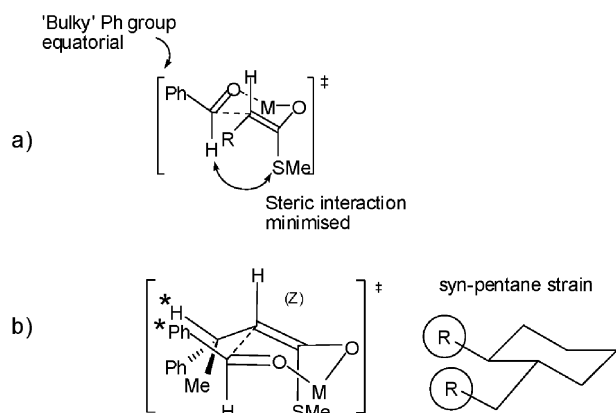
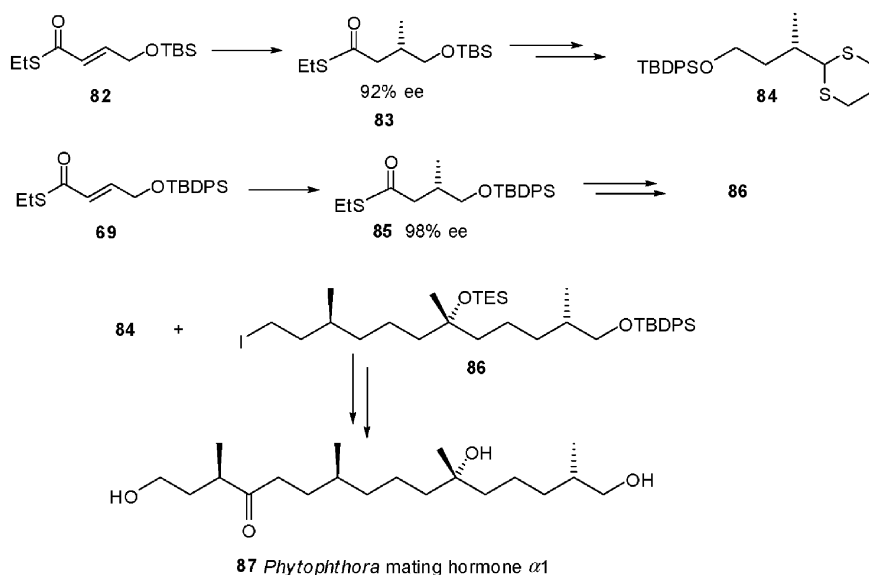


Fig. 42 Models to rationalize the *syn,syn* selectivity.

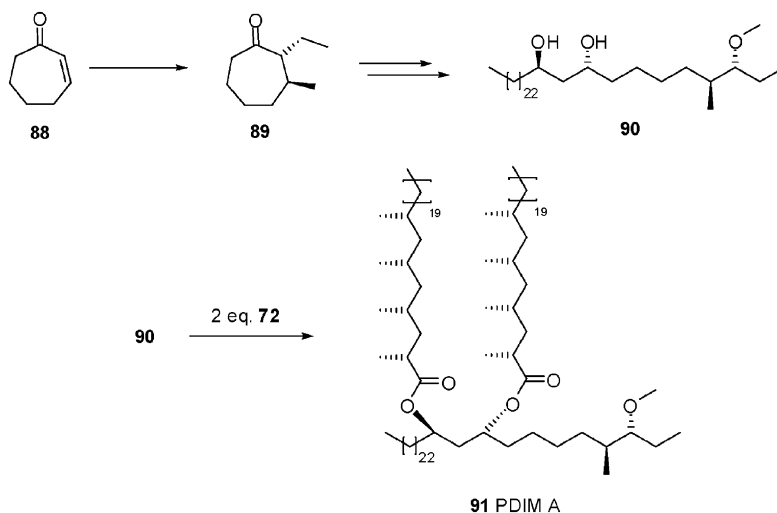
between the phenyl substituent on the aldehyde and the chiral enolate, would favour a *Si*-facial attack, resulting in the preponderant formation of the *syn,syn* diastereomer (Fig. 42b)

The versatile α,β -unsaturated thioesters can also be used in the synthesis of compounds possessing an array of 1,5-stereogenic centers such as *Phytophthora* mating hormone $\alpha 1$ **87**.¹³⁸ The dithiane moiety **84** was synthesized in a 5 step procedure starting from **82**, including a 1,4-addition of methylmagnesium bromide to **82**, resulting in **83** in 92% ee. Fragment **86** was also obtained in a 10 step procedure from the α,β -unsaturated thioester **69** after conjugate addition of methylmagnesium bromide, giving **85** in 98% ee. *Phytophthora* mating hormone $\alpha 1$ **87** was synthesized from **86** and **84** using a dithiane coupling strategy followed by deprotection of the alcohol moieties in an overall 8.1% yield after 15 steps (Scheme 64).

Finally, the asymmetric total synthesis of PDIM A **91**, a virulent factor of *Mycobacterium tuberculosis* has been developed in our group (Scheme 65).¹³⁹ Starting from



Scheme 64 Synthesis of *Phytophthora* mating hormone $\alpha 1$.



Scheme 65 Total synthesis of PDIM A.

cycloheptenone **88**, ketone **89** was obtained by copper-catalyzed asymmetric conjugate addition of dimethylzinc followed by *in situ trans*-ethylation with 95% ee and a *cis* : *trans* ratio > 20 : 1. Phthiocerol was then synthesized from **89** in an overall 5.6% yield after 14 steps. PDIM A **91** was finally obtained by esterification of mycrocercic acid **72** with phthiocerol **90**.

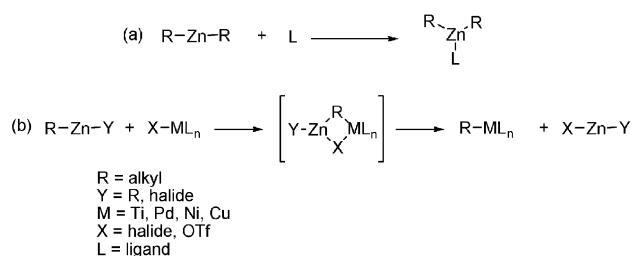
6. Mechanistic studies

The challenge of developing a general enantioselective catalyst for this useful class of reactions has led, over the last two decades, to a widespread screening of chiral ligands. Excellent results have been obtained in particular using organozinc reagents, organomagnesium reagents and, more recently, organoaluminium compounds. Although there is a wealth of earlier structural and mechanistic information on organocuprate chemistry,¹⁴⁰ much less effort has been directed to the elucidation of the mechanism of this catalytic asymmetric transformation, as well as the structure of the actual catalytically active species, despite the help such information can offer in the systematic study of ligand optimization. In this section we present an overview of studies of organometallic reagents involved in the copper-catalyzed asymmetric conjugate addition reactions, which provides insight into the reaction mechanisms involved.

6.1 Dialkylzinc

6.1.1 Phosphorus ligands. Over the past decade, enantioselective carbon–carbon bond formation using organozinc reagents has gained a prominent role in the area of 1,2-additions^{127,141} and conjugate addition.^{1,16,124} Although dialkylzinc reagents show low reactivity with enones, effective catalysis has been achieved by several ligands and transition metal complexes. The catalytic effect can be explained either by changes in geometry and bond energy of the zinc reagent upon coordination with an appropriate ligand (a) or by alkyl transfer to another metal (b) (Scheme 66).

Despite the large number of ligands described, little is known about the structure of the precatalytic complex that forms upon mixing of the copper salt (Cu(II) or Cu(I)) and the chiral ligand. To date only three crystal structures of copper(I) complexes with less selective phosphoramidites have been reported.¹⁴² The first example was reported in 1996: a copper-complex formed from CuI and MonoPhos **L1** was recrystallized from benzene affording a stable, albeit catalytically inactive monomeric complex in which three ligands are coordinated to the copper atom (Fig. 43a).¹³



Scheme 66

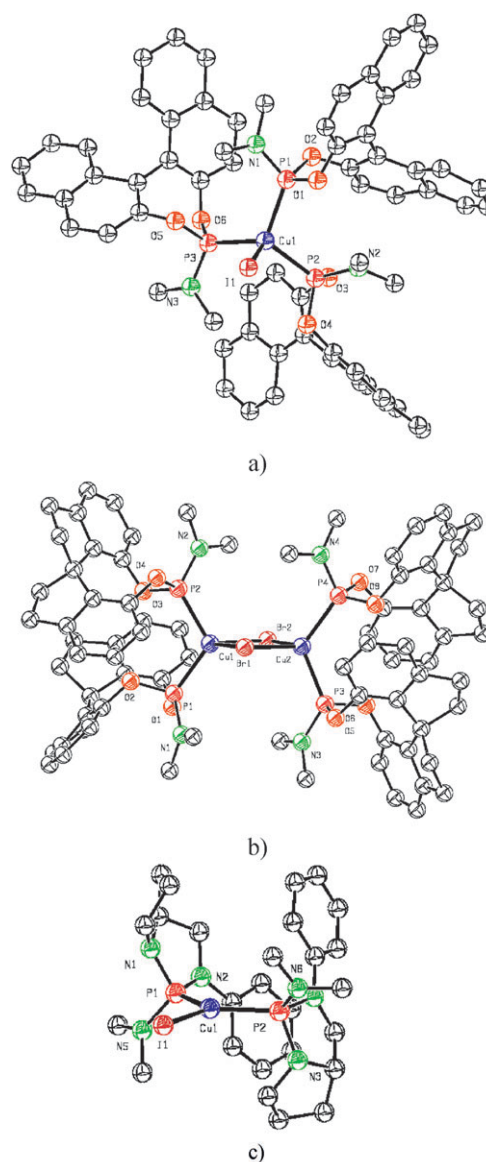


Fig. 43 X-Ray structures of complexes of copper(I) bearing phosphoramidite ligands.

In the case of the complex studied by Shi *et al.* the X-ray analysis showed the existence of a C_2 -symmetric dimer connected by bromide bridges.¹⁴³ Moreover each copper atom is coordinated to two molecules of the spiro phosphoramidite **L46** (Fig. 43b). A crystal structure clearly showing a ligand : copper ratio of 2 : 1 and a trigonal planar arrangement around Cu was obtained in 2004 by Schrader *et al.* (Fig. 43c).¹⁴⁴ The addition of a large excess of diethylzinc and cyclohexenone to this precatalyst, formed from CuI and a phosphorus triamide ligand, started the conjugate addition proving the activity of the complex. Recently, the first study on the precatalytic copper complex with phosphoramidite ligands in solution has appeared. Zhang and Gschwind investigated the structures of the complexes formed from CuCl and the phosphoramidite ligands **L8** and **L32**, (Fig. 44) in $CDCl_3$.¹⁴⁵ A ratio of 2 : 1 between copper and ligand was chosen, in accordance with the optimal ratio based on synthetic procedures.¹⁴⁶

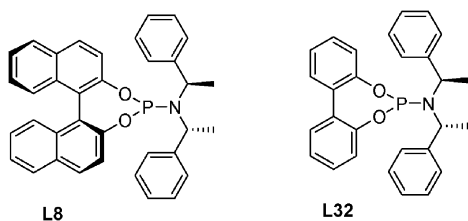


Fig. 44 Phosphoramidite ligands.

CDCl_3 was taken as solvent of choice because, in this solvent, only a single copper species could be detected. This experimental evidence is in agreement with the strong solvent effect observed in this type of catalysis.^{16,146,147} By combining information from ^{31}P -NMR spectroscopy, mass spectrometry and elemental analysis, a mixed trigonal/tetrahedral configuration of the precatalytic complex of general formula $[\text{L}_3\text{Cu}_2\text{Cl}_2]$ was proposed (Fig. 45). Such a stoichiometry can explain why ratios of ligand to copper lower than 1.5 : 1 were leading to reduced ee values.¹⁶ The presence of 3 equiv. of ligand can account for the negative nonlinear effect observed,¹⁴⁶ assuming that the copper complex formed from different enantiomers of the ligand may lead to an active catalyst which generates racemic product. Moreover the aggregation level of the complex and the presence of bridging anions may account, respectively, for the influence of the solvent and the dependence on the copper salt used.

Several copper salts have been tested in the 1,4-addition of diorganozincs to α,β -unsaturated systems. Optimal results have been obtained with $\text{Cu}(\text{OTf})_2$ as well as CuTC ,⁴³ $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and Cu naphthenate.¹⁴⁶ It has been shown that both Cu(I) and Cu(II) salts can be used with comparable results: for example CuOTf and $\text{Cu}(\text{OTf})_2$ show the same activity but $\text{Cu}(\text{OTf})_2$ has a better solubility in organic solvents and is more convenient to handle.^{14,16} *In situ* reduction of Cu(II) to Cu(I) by R_2Zn is presumed to occur.^{14,148} A first experimental proof of this assumption has been reported in 1999 by Chan¹⁴⁹ who has shown by ^{31}P -NMR that a new phosphorus species appears upon addition of diethylzinc to a $\text{Cu}(\text{OTf})_2$ -diphosphite solution. This was proposed to be the LCuEt species. More recently both Schrader¹⁴⁴ and Piarulli¹⁵⁰ observed, using EPR spectroscopy, in the reaction of $\text{Cu}(\text{OTf})_2$ with an excess of Et_2Zn complete conversion of paramagnetic Cu(II) to the diamagnetic Cu(I).

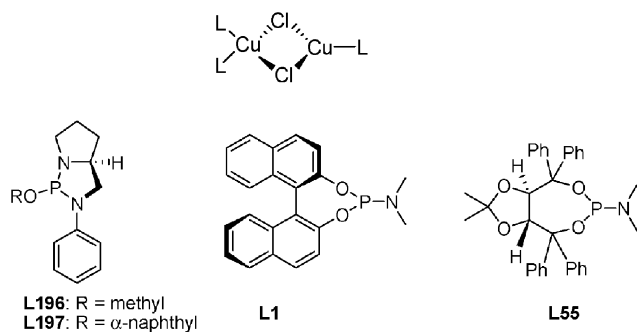
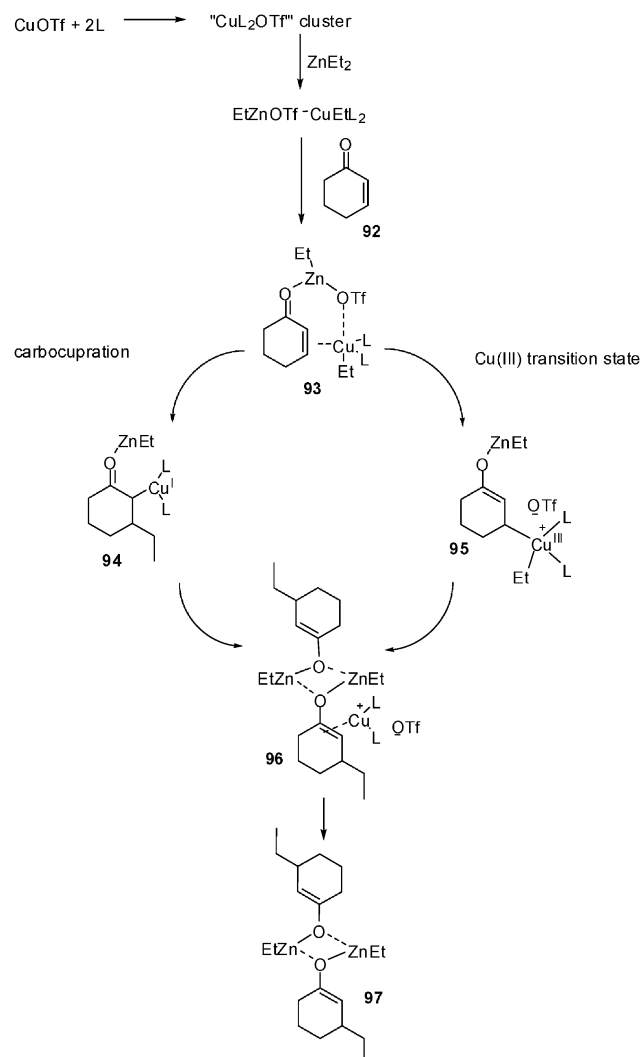


Fig. 45 (a) Precatalytic complex in CDCl_3 . (b) Ligands used by Schrader in kinetic studies.

By analogy with organocuprate¹⁴⁰ and zincate chemistry,¹⁵¹ Feringa *et al.* postulated for the first time in 1997 a similar mechanism for the copper-catalyzed organozinc addition. First alkyl transfer^{151,152} from the organozinc reagent to the copper centre is assumed (Scheme 67). Coordination of the zinc to the carbonyl function (hard–hard interaction) and π -complexation of the copper to the double bond of the enone **92** (soft–soft interaction) results in complex **93**.

Considering the high levels of enantioselectivity reached in this reaction, it is possible that species **93** is a bridged bimetallic complex in which the conformation of the enone is fixed. Both Alexakis and Noyori have proposed that, prior to the alkyl transfer, complex **93** reacts with a molecule of diethylzinc to generate a highly reactive Cu/Zn cluster (not shown).^{146,153}

At this point two reaction pathways are possible: the carbocupration mechanism involving **94** in which the alkyl transfer occurs by means of a 1,2-migratory insertion or an oxidative addition–reductive elimination mechanism in which a 3-cupro(III) enolate **95** is formed.



Scheme 67 Proposed mechanistic cycle of 1,4-addition of diethylzinc to cyclohexenone.

In the first case the stereochemistry of the product should be established in the formation of the α -cuprio(i) ketone **94** by alkyl transfer to the favourable π -face of complex **93**. For the Cu(III) intermediate pathway the formation of two diastereomeric enolates **95** is assumed: a selective reductive elimination should determine the enrichment in one of the two enantiomers.¹⁵⁴

Regardless of the mechanism both reaction pathways generate, in the end, the copper-bound enolate **96** as an intermediate which releases the zinc enolate **97** in its thermodynamically stable dimeric form.¹⁵³

Unfortunately, to date experimental evidence to discriminate between the two above mentioned mechanisms has not been reported. Kinetic studies carried out by Schrader support both a carbocupration and a rate-limiting reductive elimination pathway. Investigations on ligand acceleration were performed with various classes of trivalent phosphorus ligands (Fig. 45) having different electronic and steric properties.¹⁴⁴

In the Cu(OTf)₂-catalyzed addition of diethylzinc to cyclohexenone both ligands **L1** and **L55** proved to provide much faster reactions than the phosphorus triamide ligands **L196/L197**. This result is in agreement with a rate-limiting reductive elimination step in which electron donation to the Cu(III) centre is required and, hence, electron-withdrawing P(III) ligands facilitate this process. By contrast, electron-donating ligands improve the nucleophilicity of the alkyl-Cu species, and should accelerate the rate of the oxidative addition step. Furthermore, for all the ligands examined, first order kinetics in substrate, Et₂Zn and catalyst were observed in accordance with the assumption that the three components form a ternary 1 : 1 : 1 π -complex in which the alkyl transfer takes place.¹⁴⁴

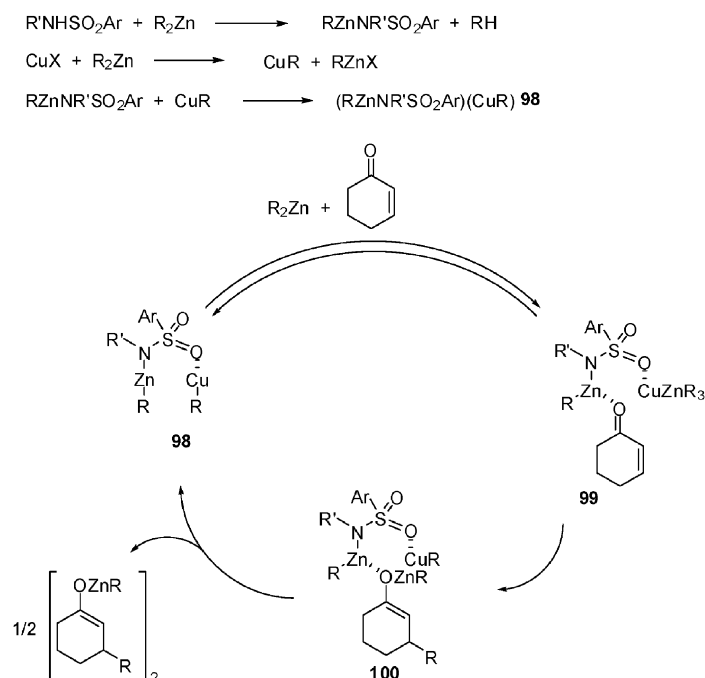
6.1.2 Non-phosphorus ligands. Different results were observed when sulfonamides,^{150,153,155} bis(oxazolines)¹⁵⁶ and

phosphoramides⁸⁷ were used. In 2000 Noyori *et al.*¹⁵³ proposed a catalytic cycle (Scheme 68) in which a bimetallic complex **98** is formed upon reaction of Et₂Zn, *N*-mono-substituted sulfonamide and the alkyl-Cu complex generated *in situ* by transmetalation. In species **98** the sulfonamide ligand serves as a three atom-spacer bridging between the Zn and Cu atoms. The ethyl group on the copper atom in **98**, however, is not reactive enough to undergo nucleophilic attack to the cyclohexenone. Species **98** is proposed to act as a bifunctional catalyst in the reaction between Et₂Zn and cyclohexenone by coordinating both the reactants. In particular, the Lewis acidic zinc atom can coordinate the carbonyl group of cyclohexanone while the cuprate moiety can interact with a molecule of Et₂Zn to form a Cu/Zn cluster **99** (species **99** is a schematic representation of the actual species that would constitute a more complex cluster).

Based on kinetic studies, the formation of a catalyst-Et₂Zn-substrate cluster **99** is assumed. The first order kinetics in both [Et₂Zn] and [substrate]_{*t*=0} suggests the alkyl transfer as the rate determining step, rather than the product release step.^{150,153} The formation of a bimetallic complex in which one molecule of ligand provides a bridge between the two metals was also proposed for bis(oxazoline) and binaphthylthiophosphoramidate type of ligands (Fig. 46).

A major difference in mechanistic interpretation compared to those based on the catalytic cycles proposed for the Cu-phosphorus ligand system discussed so far, arises from the analysis of the ¹²C/¹³C isotope effect which suggests a concerted mechanism for the alkyl transfer (Fig. 47).¹⁵⁵

In 2004 Gennari and Piarulli¹⁵⁰ studied the 1,4-addition of Et₂Zn to cyclohexenone catalyzed by Cu(OTf)₂ and ligand **L198** (Scheme 69). The authors proposed structure **102** for the complex formed upon reaction of Cu(OTf)₂ and the Schiff base **L198**. Reaction of **102** with an excess of Et₂Zn yields a



Scheme 68 Proposed mechanism for the copper-catalyzed 1,4-addition of zinc reagents using monosubstituted sulfonamide ligand.

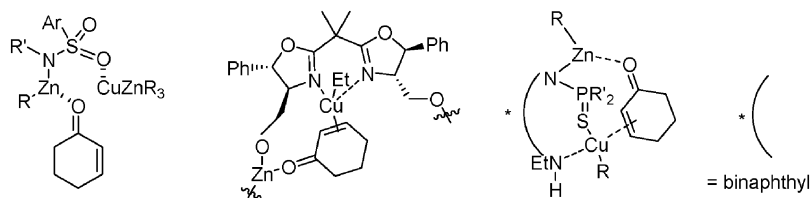


Fig. 46 Dinuclear cuprate species.

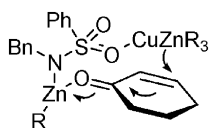


Fig. 47 Proposed intermediate complex.

catalytically active species **103**, which can transfer the ethyl group to the β -position of the cyclohexenone following first order kinetics. The resulting copper species **104** can then react with Et_2Zn to regenerate the active catalyst **103**.

The lack of a general mechanistic insight for the asymmetric conjugate addition of these organozinc reagents can partly be attributed to the sensitivity of the reaction itself to almost any variation in the reaction parameters.¹⁶

6.2 Organomagnesium reagents

The higher reactivity of Grignard reagents in comparison with organozinc reagents has hampered for a long time the development of highly efficient copper-catalyzed enantioselective methods for the conjugate addition to α,β -unsaturated compounds. Competition between 1,2- and 1,4-addition is often responsible for lower selectivity while the presence of a fast uncatalyzed reaction or catalysis by free copper salts decreases the level of enantiocontrol. Moreover, the existence of different competing organometallic complexes in solution, as

usually observed in cuprate chemistry, rendered the design of efficient catalytic systems more difficult.

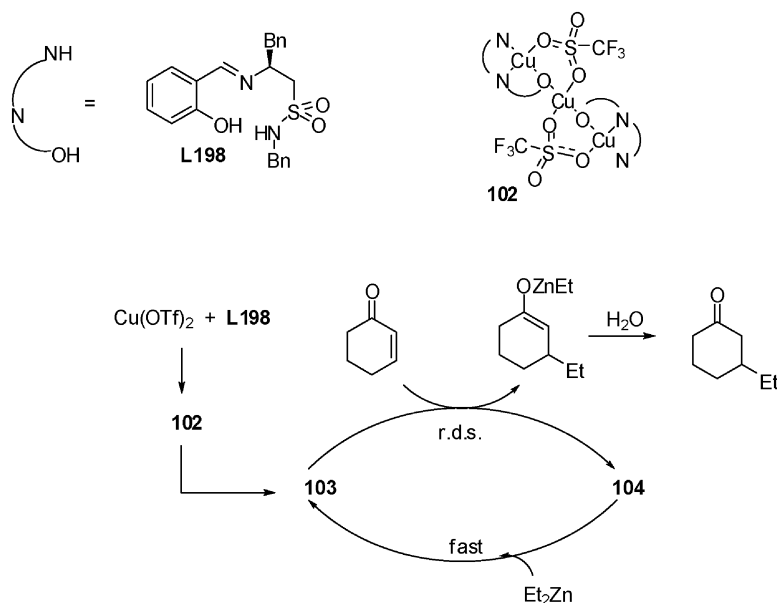
Recently, Feringa *et al.* developed the first highly enantioselective method for the conjugate addition of Grignard reagents to carbonyl compounds based on the use of catalytic amounts of Cu(I) salts and chiral ferrocenyl diphosphine ligands, such as Josiphos **L65** and Taniaphos **L64**. This method proved to be extremely efficient for a broad range of substrates including cyclic and acyclic enones, enoates and thioenates (Scheme 70).^{45–48,135}

Inspired by these excellent selectivities, a detailed mechanistic study of the copper catalyzed conjugate addition of Grignard reagents was undertaken.¹⁵⁷

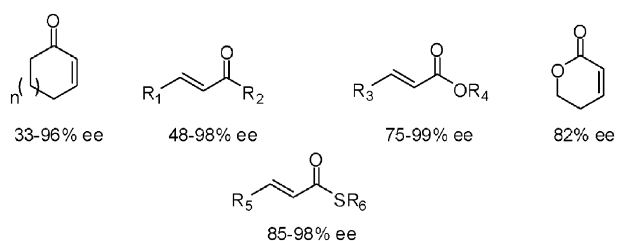
The air stable complexes **105** and **106** were prepared by addition of equimolar amounts of copper(I) salt and the chiral ligands **L65** and rev-**L65**, respectively, in the appropriate solvent (Scheme 71).

Interestingly, a solvent-dependent equilibrium between dinuclear (**105** or **106**) and mononuclear (**105'** or **106'**) species was established in solution.⁴⁷ The crystal structure of the dinuclear complex **106a**, prepared from $\text{CuBr}\cdot\text{SMe}_2$ and rev-**L65**, was obtained.^{157,158} the asymmetric unit consists of one moiety of a dinuclear copper complex, which is bridged by two Br atoms resulting in a C_2 -symmetric unit. A molecule of water is also present in the cell (Fig. 48).

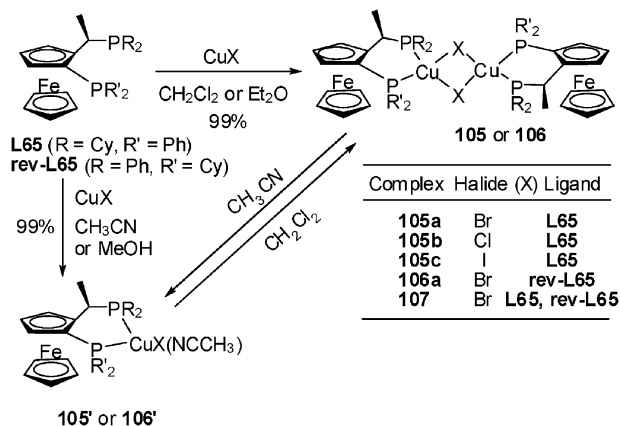
The X-ray structure of the mononuclear complex **105a'** (Fig. 49) and of the hetero-dinuclear complex **107** (Fig. 50),



Scheme 69 Proposed mechanism for the 1,4-addition of diethylzinc to cyclohexenone.



Scheme 70 Enantioselectivities obtained in 1,4-addition of Grignard reagents to α,β -unsaturated carbonyl compounds.



Scheme 71 Solvent-dependent equilibrium between dinuclear and mononuclear species.

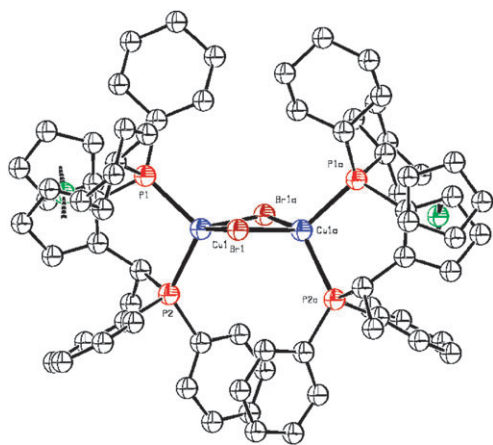


Fig. 48 Crystal structure of the dinuclear complex prepared from $\text{CuBr}\cdot\text{SMe}_2$ and rev-L65.

prepared from (*R,S*)-L65, (*S,R*)-rev-L65 and $\text{CuBr}\cdot\text{SMe}_2$ in the ratio 1 : 1 : 2, were also obtained.

Electrochemical studies were performed in order to obtain information on the different electronic properties of the copper(I) complexes **105** and **106** and the effect of ligand and halide variation. The copper complexes **105a–c**, formed from CuBr , CuCl and CuI , respectively, gave almost identical electrochemistry while significant differences were observed in the redox properties of the copper(I) centres upon ligand variation. The copper complex **106a**, for example, undergoes oxidation more easily than complex **105a** because it is more

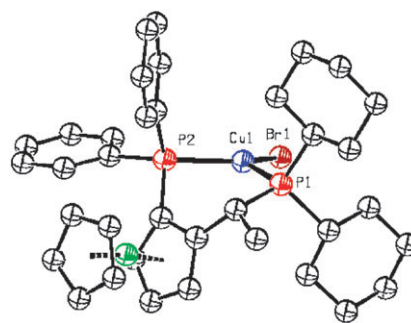


Fig. 49 Crystal structure of the mononuclear complex prepared from (*R,S*)-L65 and $\text{CuBr}\cdot\text{SMe}_2$.

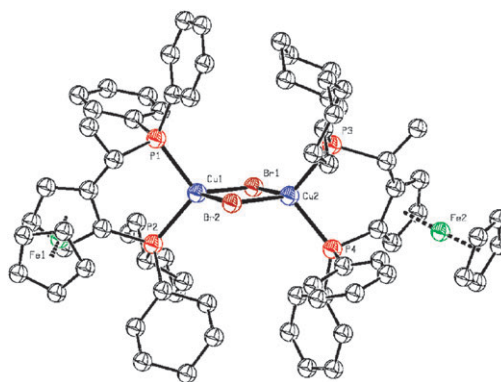
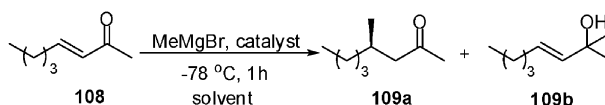


Fig. 50 Crystal structure of the hetero-dinuclear complex prepared from (*R,S*)-L65, (*S,R*)-rev-L65 and $\text{CuBr}\cdot\text{SMe}_2$.

electron rich. This finding suggests that the difference in reactivity may be explained in terms of the energy match between substrate and catalyst. The influence of the solvent and the halide was also investigated for the addition of MeMgBr to octenone under three different sets of conditions (Scheme 72): (1) in the absence of catalyst, (2) using 5 mol% of $\text{CuBr}\cdot\text{SMe}_2$, (3) in the presence of 5 mol% of chiral complexes **105a–c**. Good results both in terms of regio- and enantioselectivity were obtained in CH_2Cl_2 , toluene, Et_2O and $t\text{BuOMe}$. The use of THF afforded mainly the 1,2-addition product **109b** while the 1,4-adduct **109a** was obtained in racemic form. The solvent dependence is probably determined primarily by the Schlenk equilibrium,¹⁵⁹ which favours the solvent-coordinated monoalkylmagnesium species $\text{EtMgBr}\cdot\text{Et}_2\text{O}$ in Et_2O and the species R_2Mg and MgBr_2 in THF.

The nature of the halide used has a remarkable effect on the outcome of the reaction. The presence of bromide either in the Grignard reagent or in the Cu(I) salt appears to be essential to achieve of high regio- and enantioselectivity. This points to a



Conditions:

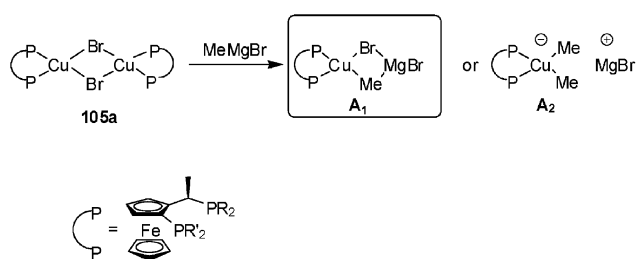
- (1) Uncatalyzed reaction: MeMgBr (1.5 eq.)
- (2) Racemic series: $\text{CuBr}\cdot\text{SMe}_2$ (5 mol%), MeMgBr (1.5 eq.)
- (3) Enantioselective series: **95a–c** (5 mol%), MeMgBr (1.1 eq.)

Scheme 72 Addition of MeMgBr to octenone.

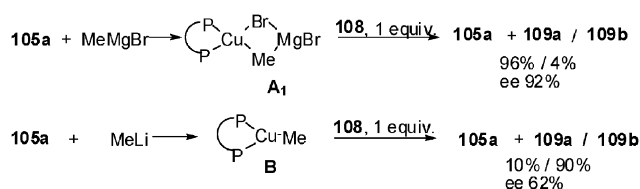
bridging role for the bromide in the anticipated dinuclear complex (*vide infra*) with precise geometrical constraints. By analogy with non-catalytic cuprate chemistry,¹⁴⁰ it is proposed that the copper complexes **105a** and **106a** undergo transmetalation upon addition of the organometallic reagent. ³¹P-NMR studies, performed at -60 °C, reveal that upon addition of MeMgBr to **105a** the formation of a new species **A** takes place. This result is compatible with the large ³¹P-NMR upfield shift assigned by Chan and co-workers to a (L)_nCuEt species, and generated from Et₂Zn, Cu(OTf)₂ and a phosphine ligand.¹⁴⁹ On the base of kinetic measurements as well as the linear relationship between the product and the catalyst enantiomeric purity, two different structures were proposed for **A** (Scheme 73). The 1 : 1 ratio between Cu and Me revealed by ¹H-NMR, excluded **A**₂ and confirmed that the active form of the catalyst is the copper complex **A**₁.

Addition of MeMgBr to **105a** gives the Cu-complex **A**₁ as the major product also in Et₂O and in toluene. On the other hand, in THF the formation of a different species **B** is observed by ³¹P-NMR spectroscopy. The role played by species **A**₁ and **B** in the catalyzed conjugate addition was investigated *via* ¹H- and ³¹P-NMR spectroscopic studies conducted after stoichiometric addition of octenone **108** to their solutions at -78 °C. Addition of an equimolar amount of **108** to **A**₁ provided the 1,4-adduct **109a** with a regioselectivity of 96% and 92% ee while the same addition to species **B** gave mainly the 1,2-addition product and only 10% of the 1,4-product with 62% ee (Scheme 74). This result is in agreement with the experiments which show a high regio- and enantioselectivity in toluene and poor selectivity in THF, indicating that the formation of **A** is essential for the successful outcome of the reaction.

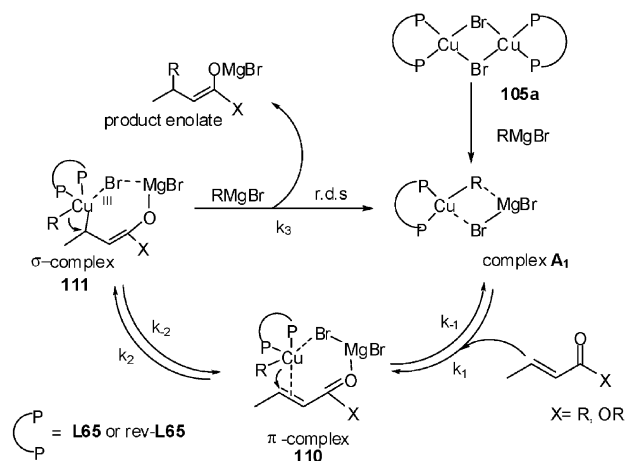
In the proposed catalytic cycle (Scheme 75) the unsaturated carbonyl compound approaches the alkylcopper complex **A**₁ from the least hindered side forming, in a reversible way, a π -complex **110** between the alkene moiety of the substrate and the copper atom; further stabilization of the π -complex **110** is provided by the complexation through Mg²⁺ and the



Scheme 73 Proposed intermediate using Grignard reagents.



Scheme 74 Stoichiometric addition of octenone to mono- and dinuclear copper-complex.

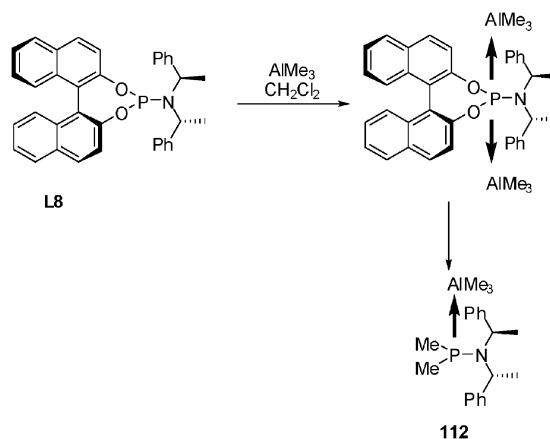


Scheme 75 Proposed catalytic cycle for the 1,4-addition of Grignard reagents to α,β -unsaturated carbonyl compounds.

carbonyl oxygen. The reversible formation of such a π -complex is supported by the ability of the catalytic system to effect *cis-trans* isomerization of the enone.^{157,160} The π -complex is probably in fast equilibrium with a Cu(III) intermediate **111**, formed *via* an intramolecular rearrangement, where the copper atom is bound to the β -carbon of the substrate. Kinetic studies suggest that the formation of the Cu(III) intermediate **111** is followed by the rate-limiting reductive elimination step in which both the substrate and Grignard reagent are involved, as suggested by the dependence of the reaction rate on their concentrations. In the case of the Grignard reagent such a dependence suggests that it acts to displace the product from the Cu(III) intermediate **111** and reforms the catalytically active complex **A**₁.

6.3 Trialkylaluminium

In recent years, in particular due to efforts in the Woodward group, it has been shown that trialkylaluminium reagents, *i.e.* Me₃Al, can be employed successfully in copper-catalyzed conjugate additions.^{38,161} Despite the high selectivities obtained, no mechanistic studies to elucidate the nature of the catalytically active species have been reported thus far. Only one example of ³¹P-NMR spectroscopic analysis has been described, although in that study the catalyst is used to



Scheme 76 Replacement of binol with methyl groups.

perform asymmetric ring opening of *meso* bicyclic hydrazines.¹⁶² The authors propose, based on ³¹P-NMR spectroscopic data, that the catalytic system Cu(OTf)₂–**L8** can undergo *in situ* replacement of the Binol moiety of **L8** with methyl groups, delivered by Me₃Al (Scheme 76). This results in the formation of a potentially active species **112**. The same behavior is observed in toluene while no modification of the phosphoramidite could be observed in THF or diethyl ether.

7. Conclusions

For decades the copper-catalyzed 1,4-addition of organometallic reagents had the reputation that it was notoriously difficult to reach high enantioselectivities in this transformation. Following breakthroughs using dialkylzinc and Grignard reagents, and recently also organoaluminium reagents, the field has advanced in the past five years to a stage where catalytic enantioselective 1,4-addition can conveniently be used in the art of complex molecule synthesis. In this review the wide variety of chiral ligands and catalysts that have emerged have been discussed with a focus on stereoselectivities, catalyst loading, ligand structure and substrate scope. A major part is devoted to trapping and tandem reactions and a variety of recent synthetic applications is illustrating the practicality and current state of the art in 1,4-addition of organometallic reagents. Finally, several mechanistic studies provide insight into the catalytic cycles involved but also clearly reveal the lack of detailed understanding, in particular regarding the mechanism of stereocontrol in these transformations. Although numerous new chiral ligands have been introduced in the last 5 years, the privileged catalysts for many of the basic substrate classes, including challenging acyclic enones and esters and demanding products such as those bearing quaternary stereocentres, have been clearly identified for the practitioner of 1,4-addition. Further advances in this field are likely to derive from detailed mechanistic studies.

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